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FILE 'CAPLUS' ENTERED AT 15:16:27 ON 16 APR 2003
L1 123 S (ANGIOTENSIN II OR AII) AND (CEREBROVASCULAR OR CEREBRAL INFA

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L1 ANSWER 1 OF 123 CAPLUS COPYRIGHT 2003 ACS
2003:286160 Relationship between oxidized low density lipoprotein and **angiotensin II** in pathogenesis of acute **cerebral infarction**. Wang, Tongyu; Zhang, Yanzong (Department of Internal Medicine, Tianjin Bohai Oil Hospital, Tianjin, 300452, Peop. Rep. China). Tianjin Yiyao, 30(9), 530-532 (Chinese) 2002. CODEN: TIYADG. ISSN: 0253-9896. Publisher: Tianjin Yixue Zazhishe.

AB The relationship between oxidized low d. lipoprotein and **angiotensin II** (AngII) in pathogenesis of acute **cerebral infarction** was studied. The levels of plasma ox-LDL and AngII were obsd. in 47 patients with acute **cerebral infarction**, 30 patients with hypertension, and 48 normal controls. The levels of plasma ox-LDL and AngII in acute **cerebral infarction** and hypertension were higher than those in controls (P <0.01). The levels of plasma ox-LDL and AngII between acute **cerebral infarction** and hypertension were not different (P >0.05). The level of AngII in acute **cerebral infarction** was higher than that in hypertension( P <0.05). The ox-LDL concn. had a pos. correlation with AngII concn. in acute **cerebral infarction**, which correlation coeff. was 0.476 5 (P <0.001). The rise of plasma ox-LDL and AngII might accelerate the processes of atherosclerosis and **cerebral infarction**, and these two factors had a pos. correlation each other.

TI Relationship between oxidized low density lipoprotein and **angiotensin II** in pathogenesis of acute **cerebral infarction**

AB The relationship between oxidized low d. lipoprotein and **angiotensin II** (AngII) in pathogenesis of acute **cerebral infarction** was studied. The levels of plasma ox-LDL and AngII were obsd. in 47 patients with acute **cerebral infarction**, 30 patients with hypertension, and 48 normal controls. The levels of plasma ox-LDL and AngII in acute **cerebral infarction** and hypertension were higher than those in controls (P <0.01). The levels of plasma ox-LDL and AngII between acute **cerebral infarction** and hypertension were not different (P >0.05). The level of AngII in acute **cerebral infarction** was higher than that in hypertension( P <0.05). The ox-LDL concn. had a pos. correlation with AngII concn. in acute **cerebral infarction**, which correlation coeff. was 0.476 5 (P <0.001). The rise of plasma ox-LDL and AngII might accelerate the processes of atherosclerosis and **cerebral infarction**, and these two factors had a pos. correlation each other.

ST oxidized low density lipoprotein **angiotensin II**: **cerebral infarction**

L1 ANSWER 2 OF 123 CAPLUS COPYRIGHT 2003 ACS
2003:168113 Normalization of Endothelial and Inducible Nitric Oxide Synthase Expression in Brain Microvessels of Spontaneously Hypertensive Rats by **Angiotensin II** AT1 Receptor Inhibition. Yamakawa, Haruki; Jezova, Miroslava; Ando, Hiromichi; Saavedra, Juan M. Journal of Cerebral Blood Flow and Metabolism, 23(3), 371-380 (English) 2003. CODEN: JCBMDN. ISSN: 0271-678X. Publisher: Lippincott Williams & Wilkins.

AB Inhibition of **angiotensin II** AT receptors protects against stroke, reducing the cerebral blood flow decrease in the periphery of the ischemic lesion. To clarify the mechanism, spontaneously hypertensive rats (SHR) and normotensive control Wistar Kyoto (WKY) rats were pretreated with the AT receptor antagonist candesartan (0.3 mg .cntdot. kg .cntdot. d ) for 28 days, a treatment identical to that which protected SHR from brain ischemia, and the authors studied middle cerebral artery (MCA) and common carotid morphol., endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) mRNA (mRNA), and protein expression in cerebral microvessels, principal arteries of the Willis polygon, and common carotid artery. The MCA and common carotid artery of SHR exhibited inward eutrophic remodeling, with decreased lumen diam. and increased media thickness when compared with WKY rats. In addn., there was decreased eNOS and increased iNOS protein and mRNA in common carotid artery, circle of Willis, and brain microvessels of SHR when compared with WKY rats. Both remodeling and alterations in eNOS and iNOS expression in SHR were completely reversed by long-term AT receptor inhibition. The hemodynamic, morphol., and biochem. alterations in hypertension assocd. with increased vulnerability to brain ischemia are fully reversed by AT receptor blockade, indicating that AT receptor activation is crucial for the maintenance of the pathol. alterations in **cerebrovascular** circulation during hypertension, and that their blockade may be of therapeutic advantage.1 1 1 1 1.

TI Normalization of Endothelial and Inducible Nitric Oxide Synthase Expression in Brain Microvessels of Spontaneously Hypertensive Rats by **Angiotensin II** AT1 Receptor Inhibition

AB Inhibition of **angiotensin II** AT receptors protects against stroke, reducing the cerebral blood flow decrease in the periphery of the ischemic lesion. To clarify. . . reversed by AT receptor blockade, indicating that AT receptor activation is crucial for the maintenance of the pathol. alterations in **cerebrovascular** circulation during hypertension, and that their blockade may be of therapeutic advantage.1 1 1 1 1.

L1 ANSWER 3 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:937235 Document No. 138:236198 Polymorphism of renin-angiotensin system genes in dialysis patients-association with **cerebrovascular** disease. Losito, Attilio; Kalidas, Kamini; Santoni, Stefania; Ceccarelli, Luigi; Jeffery, Steve (Policlinico Monteluce, UO Nefrologia e Dialisi, Perugia, I-06122, Italy). Nephrology, Dialysis, Transplantation, 17(12), 2184-2188 (English) 2002. CODEN: NDTREA. ISSN: 0931-0509. Publisher: Oxford University Press.

AB Polymorphisms of genes of the renin-angiotensin system (RAS) have been found in assocn. with **cerebrovascular** and cardiovascular diseases in the general population. In dialysis patients, RAS gene polymorphisms have been studied in combination and sep. and have yielded conflicting results. In this study we have analyzed, in 160 dialysis patients, the distribution of the following genetic polymorphisms: M235T and T174M of the angiotensinogen gene, A1166C of the **angiotensin II** type 1 receptor gene and the insertion/deletion (I/D) of the ACE gene. The assocn. of these polymorphisms with **cerebrovascular** and cardiovascular diseases was also tested. Healthy blood donors and hospital staff (169) were the control group for the distribution of the polymorphisms. The distribution of the polymorphisms in dialysis patients as a whole did not differ significantly from that of healthy controls. However, for patients with severe **cerebrovascular** disease, 70% carried the D allele compared with 52% of patients without **cerebrovascular** disease (P=0.035). We also found that the degree of carotid artery stenosis was significantly correlated with the presence of the ACE 'D' allele in subjects on dialysis (P=0.0348). The distribution of RAS genes in dialysis patients is similar to that of the normal population. The presence of the D allele of ACE gene is assocd. with **cerebrovascular** disease and the degree of carotid artery stenosis. We postulate that the ACE gene polymorphism is a risk factor for **cerebrovascular** disease in dialytic patients.

TI Polymorphism of renin-angiotensin system genes in dialysis patients-association with **cerebrovascular** disease

AB Polymorphisms of genes of the renin-angiotensin system (RAS) have been found in assocn. with **cerebrovascular** and cardiovascular diseases in the general population. In dialysis patients, RAS gene polymorphisms have been studied in combination and sep. . . . 160 dialysis patients, the distribution of the following genetic polymorphisms: M235T and T174M of the angiotensinogen gene, A1166C of the **angiotensin II** type 1 receptor gene and the insertion/deletion (I/D) of the ACE gene. The assocn. of these polymorphisms with **cerebrovascular** and cardiovascular diseases was also tested. Healthy blood donors and hospital staff (169) were the control group for the distribution. . . in dialysis patients as a whole did not differ significantly from that of healthy controls. However, for patients with severe **cerebrovascular** disease, 70% carried the D allele compared with 52% of patients without **cerebrovascular** disease (P=0.035). We also found that the degree of carotid artery stenosis was significantly correlated with the presence of the. . . is similar to that of the normal population. The presence of the D allele of ACE gene is assocd. with **cerebrovascular** disease and the degree of carotid artery stenosis. We postulate that the ACE gene polymorphism

L1 ANSWER 3 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
is a risk factor for **cerebrovascular** disease in dialytic patients.

ST ACE AT1 receptor angiotensinogen gene polymorphism **cerebrovascular** disease hemodialysis

IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(AGT; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(AT1 receptors; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(Ace; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Allele frequency
Genetic polymorphism
Genotypes
Human
Hypertension
Susceptibility (genetic)
(angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Artery, disease
(carotid, stenosis; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Brain, disease
(**cerebrovascular**; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Cardiovascular system
(disease; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Kidney, disease
(failure, chronic; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Dialysis
(hemodialysis; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

IT Angiotensin receptors

L1 ANSWER 3 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type AT1; angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)
IT 9015-82-1, Angiotensin-converting enzyme 11002-13-4, Angiotensinogen
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(angiotensinogen, angiotensin AT1 receptor and ACE genes polymorphisms assocn. with **cerebrovascular** disease in dialysis patients)

L1 ANSWER 4 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
losartan effect on cognitive function)
IT 114798-26-4, Losartan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**angiotensin II** receptor antagonist losartan effect on cognitive function)

L1 ANSWER 4 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:930570 Document No. 138:11276 Does the **angiotensin II** receptor antagonist losartan improve cognitive function?. Tedesco, Michele A.; Ratti, Gennaro; Di Salvo, Giovanni; Natale, Francesco (Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples, Naples, Italy). Drugs & Aging, 19(10), 723-732 (English) 2002. CODEN: DRAGE6. ISSN: 1170-229X. Publisher: Adis International Ltd..
AB Newer classes of antihypertensive agents, such as **angiotensin II** receptor antagonists, may offer benefits to patients in addn. to their ability to lower blood pressure. It is accepted that chronic hypertension contributes to the development of **cerebrovascular** and cardiovascular disease, and several studies have demonstrated a link between hypertension and reduced cognitive function, esp. in patients not receiving antihypertensive medication. In an initial clin. trial, the **angiotensin II** receptor antagonist losartan was shown to improve cognitive function in patients with hypertension, including in those who were elderly (up to 73 yr of age). This effect cannot be explained by a redn. in blood pressure alone and is likely to involve interactions with the diverse biol. actions of the renin-angiotensin system. Improving or maintaining cognitive function in patients with hypertension may translate into economic benefits beyond those expected due to blood pressure control, and would result in considerable quality-of-life benefits for the aging population.
TI Does the **angiotensin II** receptor antagonist losartan improve cognitive function?
AB Newer classes of antihypertensive agents, such as **angiotensin II** receptor antagonists, may offer benefits to patients in addn. to their ability to lower blood pressure. It is accepted that chronic hypertension contributes to the development of **cerebrovascular** and cardiovascular disease, and several studies have demonstrated a link between hypertension and reduced cognitive function, esp. in patients not receiving antihypertensive medication. In an initial clin. trial, the **angiotensin II** receptor antagonist losartan was shown to improve cognitive function in patients with hypertension, including in those who were elderly (up. . .
ST **angiotensin II** receptor antagonist losartan cognition hypertension antihypertensive elderly
IT Antihypertensives
Cognition
Human
Hypertension
(**angiotensin II** receptor antagonist losartan effect on cognitive function)
IT Angiotensin receptor antagonists
(**angiotensin II**; **angiotensin II** receptor antagonist losartan effect on cognitive function)
IT Aging, animal
(elderly; **angiotensin II** receptor antagonist

L1 ANSWER 5 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:824769 AII receptor antagonists and **cerebrovascular** protection. Eguchi, Kazuo; Kario, Nanaomi; Shimada, Kazuyuki (Dept. of Cardiology, Jichi Medical School, Japan). Ketsuatsu, 9(8), 782-786 (Japanese) 2002. CODEN: KETSAH. ISSN: 1340-4598. Publisher: Sentan Igakusha.
AB Unavailable
TI AII receptor antagonists and **cerebrovascular** protection

L1 ANSWER 6 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:813926 Document No. 137:304829 Enantiomers of N-[[2'-[[(4,5-dimethyl-3-isoxazolyl) amino]sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide. Hughes, David E.; Seidenberg, Beth C. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2002083130 A1 20021024, 24 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US11992 20020412. PRIORITY: US 2001-PV284080 20010416.

AB Endothelin antagonist N-[[2'-[[(4,5-dimethyl-3-isoxazolyl)amino] sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide surprisingly exists as separable enantiomeric atropisomers. The (+)-dextrorotatory atropisomer demonstrates remarkably higher potency than either the (-)-levorotatory atropisomer or the racemate. The (+)-dextrorotatory atropisomer is suitable for treatment of endothelin-related disorders, such as hypertension, renal diseases, atherosclerosis, restenosis, congestive heart failure, diabetic nephropathy, cancer, asthma, etc., alone or in combination with, e.g., angiotensin, renin, or ACE inhibitors, diuretics, cardiac glycosides, antiplatelet agents, etc.

IT Angiotensin receptor antagonists
(**angiotensin II**, combination with; therapeutic uses of enantiomers of biphenyl isoxazole sulfonamide deriv. as endothelin antagonists)

IT Meninges
(**subarachnoid hemorrhage**; therapeutic uses of enantiomers of biphenyl isoxazole sulfonamide deriv. as endothelin antagonists)

L1 ANSWER 7 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:812991 Document No. 137:332652 Angiotensin-converting enzyme inhibitors: Are there credible mechanisms for beneficial effects in diabetic neuropathy?. Malik, Rayaz A.; Tomlinson, David R. (Department of Medicine, Manchester Royal Infirmary, Manchester, M13 9WL, UK). International Review of Neurobiology, 50(Neurobiology of Diabetic Neuropathy), 415-430 (English) 2002. CODEN: IRNEAE. ISSN: 0074-7742. Publisher: Academic Press.

AB A review. ACE inhibitors have surpassed all predictions for their widespread use in clin. medicine. Initially deemed useful only in a select group of patients with renovascular hypertension (Di Giulio et al., 1981), they now constitute the panacea for the treatment of diabetes and its complications, ischemic heart and **cerebrovascular** disease, and nephropathy from a variety of causes. The pharmacol. of ACE inhibition is complex and provides for a no. of major interactions with pathogenetically relevant pathways resulting in human diabetic neuropathy. This article reviews the vascular basis for diabetic neuropathy and discusses clin. trials utilizing ACE inhibitor therapy. The physiol. of **Angiotensin II** and the vasodilatory effect of ACE inhibitors are reviewed along with the effect on the renin/angiotensin system. (c) 2002 Academic Press.

AB . . . Giulio et al., 1981), they now constitute the panacea for the treatment of diabetes and its complications, ischemic heart and **cerebrovascular** disease, and nephropathy from a variety of causes. The pharmacol. of ACE inhibition is complex and provides for a no.. . . This article reviews the vascular basis for diabetic neuropathy and discusses clin. trials utilizing ACE inhibitor therapy. The physiol. of **Angiotensin II** and the vasodilatory effect of ACE inhibitors are reviewed along with the effect on the renin/angiotensin system. (c) 2002 Academic. . .

IT 9015-94-5, Renin, biological studies 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(angiotensin-converting enzyme inhibitors for diabetic neuropathy patients)

L1 ANSWER 8 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:755214 Document No. 137:263024 Preparation of N-isoxazolyl biphenylsulfonamides and related compounds as dual **angiotensin II** and endothelin receptor antagonists.. Murugesan, Natesan; Tellew, John E.; Macor, Jhon E.; Gu, Zhengxiang (USA). U.S. Pat. Appl. Publ. US 2002143024 A1 20021003, 206 pp., Cont.-in-part of U.S. Ser. No. 643,640, abandoned. (English). CODEN: USXXCO. APPLICATION: US 2000-737201 20001214. PRIORITY: US 1998-PV91847 19980706; US 1999-345392 19990701; US 1999-464037 19991215; US 2000-481197 20000111; US 2000-513779 20000225; US 2000-604322 20000626; US 2000-643640 20000822.

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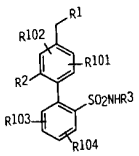


I

AB Title compds. (I; R1 = specified oxoimidazolyl, pyridoimidazolyl, pyridylamino, pyridyloxy, triazolyl, quinolinyloxy, etc.; R2 = H, halo, CHO, (halo)alkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxy, cyano, OH, NO2, etc.; R3 = heteroaryl; R101-R104 = H, halo, CHO, alkyl, haloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, cyano, OH, hydroxyalkyl, NO2, etc; with provisos) were prepd. as dual **angiotensin II** and endothelin receptor antagonists for treatment of hypertension and other diseases (no data). Thus, 4-BrC6H4CH2OH was coupled with [2-[[(4,5-dimethyl-3-isoxazolyl)[(2-methoxyethoxy)methyl]amino]sulfonyl]phenyl]boronic acid to give N-(4,5-dimethyl-3-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide (66%). This was brominated to give the 4'-bromomethyl deriv. (90%), reacted with 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride, and deprotected (49% for two steps) to give 4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-[1,1'-biphenyl]-2-sulfonamide.

TI Preparation of N-isoxazolyl biphenylsulfonamides and related compounds as dual **angiotensin II** and endothelin receptor antagonists.

AB . . . alkyl, haloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, cyano, OH, hydroxyalkyl, NO2, etc; with provisos) were prepd. as dual **angiotensin II** and endothelin receptor antagonists for treatment of hypertension and other diseases (no data). Thus, 4-BrC6H4CH2OH was coupled with [2-[[(4,5-dimethyl-3-isoxazolyl)[(2-methoxyethoxy)methyl]amino]sulfonyl]ph

L1 ANSWER 8 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

enyl]boronic acid. . . .
254746-03-7P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2'-(3-fluoropropyl)-4'-(hydroxymethyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-04-8P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2'-(3-fluoropropyl)-4'-[[(methylsulfonyl)oxy]methyl]-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-06-0P 254746-07-1P, Methanesulfonic acid, trifluoro-, 2-acetyl-4-bromophenyl ester 254746-08-2P, Methanesulfonic acid, trifluoro-, 4-bromo-2-(1,1-difluoroethyl)phenyl ester 254746-09-3P, Methanesulfonic acid, trifluoro-, 2-(1,1-difluoroethyl)-4-formylphenyl ester 254746-10-6P, [1,1'-Biphenyl]-2-sulfonamide, 2'-(1,1-difluoroethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-formyl-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-11-7P, [1,1'-Biphenyl]-2-sulfonamide, 2'-(1,1-difluoroethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-12-8P, [1,1'-Biphenyl]-2-sulfonamide, 2'-(1,1-difluoroethyl)-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[(methylsulfonyl)oxy]methyl]-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-13-9P 254746-14-0P, Benzoic acid, 4-bromo-3-(2,2,2-trifluoroethyl)-, methyl ester 254746-15-1P, [1,1'-Biphenyl]-4-carboxylic acid, 2'-[[(3,4-dimethyl-5-isoxazolyl)[[2-[(trimethylsilyl)oxy]ethoxy]methyl]amino]sulfonyl]-2-(2,2,2-trifluoroethyl)-, methyl ester 254746-16-2P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-2'-(2,2,2-trifluoroethyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-18-4P 254746-19-5P, Benzene, 1-bromo-4-methyl-2-(2-methylpropoxy)- 254746-20-8P, Benzene, 1-bromo-4-(bromomethyl)-2-(2-methylpropoxy)- 254746-21-9P, 1,3-Diazaspiro[4.4]non-1-en-4-one, 3-[[4-bromo-3-(2-methylpropoxy)phenyl]methyl]-2-butyl- 254746-22-0P 254746-23-1P, Benzene, 1-bromo-2-(2-methoxyethoxy)-4-methyl- 254746-24-2P, Benzene, 1-bromo-4-(bromomethyl)-2-(2-methoxyethoxy)- 254746-25-3P, 1,3-Diazaspiro[4.4]non-1-en-4-one, 3-[[4-bromo-3-(2-methoxyethoxy)phenyl]methyl]-2-butyl- 254746-26-4P 254746-27-5P, Benzonitrile, 4-bromo-3-(1-butenyl)- 254746-28-6P, Benzonitrile, 4-bromo-3-butyl- 254746-29-7P, Benzaldehyde, 4-bromo-3-butyl- 254746-30-0P, [1,1'-Biphenyl]-2-sulfonamide, 2'-butyl-N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-31-1P, [1,1'-Biphenyl]-2-sulfonamide, 2'-butyl-N-(3,4-dimethyl-5-isoxazolyl)-4'-[[(methylsulfonyl)oxy]methyl]-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-32-2P 254746-33-3P, Boronic acid, [2-[[(3-methyl-5-isoxazolyl)[[2-[(trimethylsilyl)oxy]ethoxy]methyl]amino]sulfonyl]phenyl]- 254746-34-4P, [1,1'-Biphenyl]-2-sulfonamide, 4'-formyl-N-(3-methyl-5-isoxazolyl)-2'-(trifluoromethyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-35-5P, [1,1'-Biphenyl]-2-sulfonamide, 4'-(hydroxymethyl)-N-(3-methyl-5-isoxazolyl)-2'-(trifluoromethyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-36-6P 254746-37-7P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-methoxyethoxy)methyl]-2'-[(methoxymethylamino)methyl]- 254746-38-8P, [1,1'-Biphenyl]-2-sulfonamide, 4'-(bromomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]-2'-[(methoxymethylamino)methyl]- 254746-39-9P

L1 ANSWER 8 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
254746-40-2P, Benzoic acid, 4-bromo-3-(hydroxymethyl)-, methyl ester 254746-41-3P, Benzoic acid, 3-[(acetyloxy)methyl]-4-bromo-, methyl ester 254746-42-4P, Benzoic acid, 4-bromo-3-[[(tetrahydro-2H-pyran-2-yl)oxy]methyl]-, methyl ester 254746-43-5P, [1,1'-Biphenyl]-4-carboxylic acid, 2'-[[(3,4-dimethyl-5-isoxazolyl)[[2-[(trimethylsilyl)oxy]ethoxy]methyl]amino]sulfonyl]-2-[[(tetrahydro-2H-pyran-2-yl)oxy]methyl]-, methyl ester 254746-44-6P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-2'-[[(tetrahydro-2H-pyran-2-yl)oxy]methyl]-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-45-7P 254746-46-8P 254746-47-9P 254746-48-0P, Benzoic acid, 3-(2-hydroxyethyl)-4-[[(trifluoromethyl)sulfonyl]oxy]-, methyl ester 254746-49-1P, [1,1'-Biphenyl]-4-carboxylic acid, 2'-[[(3,4-dimethyl-5-isoxazolyl)[[2-[(trimethylsilyl)oxy]ethoxy]methyl]amino]sulfonyl]-2-(2-hydroxyethyl)-, methyl ester 254746-50-4P, [1,1'-Biphenyl]-4-carboxylic acid, 2'-[[(3,4-dimethyl-5-isoxazolyl)[[2-[(trimethylsilyl)oxy]ethoxy]methyl]amino]sulfonyl]-2-(2-fluoroethyl)-, methyl ester 254746-51-5P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-2'-(2-fluoroethyl)-4'-(hydroxymethyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-52-6P 254746-53-7P, [1,1'-Biphenyl]-4-carboxylic acid, 2'-[[(3,4-dimethyl-5-isoxazolyl)[[2-[(trimethylsilyl)oxy]ethoxy]methyl]amino]sulfonyl]-2-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]-, methyl ester 254746-54-8P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-2'-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-55-9P, Benzonitrile, 4-bromo-3-(3-methyl-1-butenyl)- 254746-56-0P, Benzonitrile, 4-bromo-3-(3-methylbutyl)- 254746-57-1P, Benzaldehyde, 4-bromo-3-(3-methylbutyl)- 254746-58-2P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-methoxyethoxy)methyl]-2'-(3-methylbutyl)- 254746-59-3P, [1,1'-Biphenyl]-2-sulfonamide, 4'-(bromomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]-2'-(3-methylbutyl)- 254746-60-6P, Benzonitrile, 4-[(2-methyl-2-propenyl)oxy]- 254746-61-7P, Benzonitrile, 4-hydroxy-3-(2-methyl-2-propenyl)- 254746-62-8P, Benzonitrile, 4-hydroxy-3-(2-methylpropyl)- 254746-63-9P, Benzaldehyde, 4-hydroxy-3-(2-methylpropyl)- 254746-64-0P, Methanesulfonic acid, trifluoro-, 4-formyl-2-(2-methylpropyl)phenyl ester 254746-65-1P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-4'-formyl-N-[(2-methoxyethoxy)methyl]-2'-(2-methylpropyl)- 254746-66-2P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-methoxyethoxy)methyl]-2'-(2-methylpropyl)- 254746-67-3P, [1,1'-Biphenyl]-2-sulfonamide, 4'-(bromomethyl)-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]-2'-(2-methylpropyl)- 254746-68-4P 254746-69-5P, Cyclopentanecarboxylic acid, 1-[(3,3-difluoro-1-oxobutyl)amino]-, methyl ester 254746-70-8P, 1,3-Diazaspiro[4.4]non-1-en-4-one, 2-(3,3-difluorobutyl)- 254746-71-9P, [1,1'-Biphenyl]-2-sulfonamide, N-(3,4-dimethyl-5-isoxazolyl)-4'-[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-(3,3,3-trifluoropropyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-72-0P, Benzoic acid, 4-bromo-3-[(1,1-dimethylethoxy)methyl]-, methyl ester 254746-73-1P, [1,1'-Biphenyl]-4-carboxylic acid, 2-[(1,1-dimethylethoxy)methyl]-2'-[[(3,4-dimethyl-5-isoxazolyl)[[2-[(trimethylsilyl)oxy]ethoxy]methyl]amino]sulfonyl]-, methyl ester 254746-74-2P, [1,1'-Biphenyl]-2-sulfonamide, 2'-[(1,1-dimethylethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4'-(hydroxymethyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-75-3P, [1,1'-Biphenyl]-2-sulfonamide, 4'-(bromomethyl)-2'-[(1,1-dimethylethoxy)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-N-[[2-[(trimethylsilyl)oxy]ethoxy]methyl]- 254746-76-4P 254746-82-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT 50-78-2, Aspirin 52-01-7, Spironolactone 10238-21-8, Glyburide 51384-51-1, Metoprolol 55142-85-3, Ticlopidine 72956-09-3, Carvedilol 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 107724-20-9, Eplerenone 113665-84-2, Clopidogrel 134523-00-5, Atorvastatin 147098-20-2, Zd-4522 147526-32-7, NK 104 150322-43-3, Cs-747
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothe

SYSTEM LIMITS
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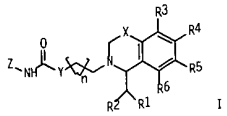
L1 ANSWER 9 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:754383 Document No. 137:262959 Preparation of 1,2,3,4-tetrahydroisoquinolinyl ureas and related derivatives as urotensin II receptor antagonists. Aissaoui, Hamed; Binkert, Christoph; Clozel, Martine; Mathys, Boris; Mueller, Claus; Nayler, Oliver; Scherz, Michael; Weller, Thomas (Actelion Pharmaceuticals Ltd., Switz.; Velker, Joerg). PCT Int. Appl. WO 2002076979 A1 20021003, 94 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-EP3131 20020320. PRIORITY: WO 2001-EP3422 20010327; WO 2001-EP9845 20010827.

GI



I

AB The invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivs. (shown as I; e.g. 1-[2-[1-(4-Fluorobenzyl)-6,8-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]ethyl]-3-(2-methylquinolin-4-yl)urea) and related compds. and their use as active ingredients in the prepn. of pharmaceutical compns. The invention also concerns related aspects including processes for the prepn. of the compds. (but not claimed), pharmaceutical compns. contg. one or more of those compds. and esp. their use as neurohormonal antagonists esp. urotensin II antagonists. In I, X = -CH2-, -CH2CH2-, -CMe2-; Y = O, NH; n = 1, 2; Z = quinolin-4-yl which may be monosubstituted with lower alkyl in the positions 2, 6, or 8, or disubstituted with lower alkyl in the positions 2,6 or 2,8; [1,8]naphthyridin-4-yl which may be substituted in position 7 with lower alkyl; pyridin-4-yl which may be substituted in position 2 with R7R8N- and addnl. in position 6 with H or lower alkyl. R1 = naphthalen-1-yl; naphthalen-2-yl; benzo[1,3]dioxol-5-yl; benzyl, or mono, di, or trisubstituted benzyl substituted in the Ph ring independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen, cyano; Ph, or mono, di- or trisubstituted Ph, substituted independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen, cyano. R2 = H, lower alkyl, aryl or forms with R1 a styryl group of E or Z geometry, whereby the Ph ring in the styryl group may be mono, di- or trisubstituted Ph, substituted independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen,

L1 ANSWER 9 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
cyano. R3, R4, R5 and R6 independently = H, cyano, hydroxy, lower alkyloxy, aralkyloxy, lower alkenyloxy, and R5 addnl. = R7R8NCO; R4 and R5 together may form with the Ph ring a five- or a six-membered ring contg. one or two O atoms; R7 and R8 independently represent H, lower alkyl, aryl, aralkyl, or together with the N form a pyrrolidine, piperidine, or morpholine ring. Test results for 4 of the claimed compds. regarding inhibition of human [125I]-urotensin II binding to a rhabdomyosarcoma cell line (IC50 = 67-550 nM) and for 2 compds. regarding inhibition of human urotensin II-induced contractions of isolated rat aortic arch (pD2' = 5.23, 5.45) are reported. Although the methods of prepn. are not claimed, a no. of examples of prepn. of intermediates and target compds. are included.

IT Angiotensin receptor antagonists
(**angiotensin II**; in combination with tetrahydroisoquinoline ureas and related deriv. urotensin II receptor antagonists for treatment of various disorders)

IT Meninges
(**subarachnoid hemorrhage**; prepn. of tetrahydroisoquinoline ureas and related derivs. as urotensin II receptor antagonists for treatment of various disorders)

L1 ANSWER 10 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:716094 Document No. 137:226612 Antihypertensive agent and cholesterol absorption inhibitor combination therapy. Nichtberger, Steven A. (Merck & Co., Inc., USA). PCT Int. Appl. WO 2002072104 A2 20020919, 29 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US6570 20020305. PRIORITY: US 2001-PV274288 20010308.

AB The invention includes methods for treating atherosclerosis and preventing atherosclerotic disease events in a hypertensive patient comprising administering to the patient a therapeutically or prophylactically effective amt. of at least one antihypertensive compd. in combination with a therapeutically effective amt. of a cholesterol absorption inhibitor. The invention also includes a compn. comprising at least one antihypertensive compd. and a cholesterol absorption inhibitor in therapeutically effective amts., and a pharmaceutically acceptable carrier.

IT Angiotensin receptor antagonists
(**angiotensin II**; antihypertensive agent and cholesterol absorption inhibitor combination therapy)

IT Brain, disease
(**cerebrovascular**; antihypertensive agent and cholesterol absorption inhibitor combination therapy)

L1 ANSWER 11 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:551882 Document No. 138:214720 Potential for antihypertensive treatment with an AT1-receptor blocker to reduce dementia in the elderly. Trenkwalder, P. (Starnberg Hospital, Department of Internal Medicine, Ludwig Maximilian University Munich, Starnberg, Germany). Journal of Human Hypertension, 16(Suppl. 3), S71-S75 (English) 2002. CODEN: JHHYEN. ISSN: 0950-9240. Publisher: Nature Publishing Group.

AB A review. Hypertension is an established risk factor for stroke and other **cerebrovascular** disorders. Both stroke and small lacunar infarcts or white matter lesions can cause cognitive impairment and dementia, and there is evidence that vascular risk factors play a major role in the development of both Alzheimer's disease and vascular dementia. Several large epidemiol. studies have shown that raised blood pressure in midlife is a strong risk factor for dementia later in life; however, blood pressure often decreases following the development of dementia. The cognitive function hypothesis proposes that elevated blood pressure increases the risk of decline of cognitive function, and that this can be reversed by active lowering of blood pressure. Evidence in support of this hypothesis comes from the Syst-Eur Dementia project, and from a no. of smaller studies. SCOPE (Study on Cognition and Prognosis in the Elderly) is a large prospective study involving almost 5000 elderly patients (age 70-89 yr), who are randomized to receive candesartan cilexetil, 8-16 mg, or placebo. Candesartan was chosen for this study because it is effective and well tolerated in elderly patients. SCOPE should provide important information on the long-term effects of AT1-receptor blocker treatment with candesartan on morbidity-including effects on cognitive function-and cardiovascular mortality in elderly hypertensive patients.

AB A review. Hypertension is an established risk factor for stroke and other **cerebrovascular** disorders. Both stroke and small lacunar infarcts or white matter lesions can cause cognitive impairment and dementia, and there is. . .

IT Angiotensin receptor antagonists
(**angiotensin II**, AT1; potential for antihypertensive treatment with AT1-receptor blocker to reduce dementia in elderly humans)

L1 ANSWER 12 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:551880 Document No. 138:214719 The renin-angiotensin system in the brain: possible therapeutic implications for AT1-receptor blockers. Culman, J.; Blume, A.; Gohlke, P.; Unger, T. (Institute of Pharmacology, Christian-Albrechts-University of Kiel, Kiel, 24105, Germany). Journal of Human Hypertension, 16(Suppl. 3), S64-S70 (English) 2002. CODEN: JHHYEN. ISSN: 0950-9240. Publisher: Nature Publishing Group.

AB A review. Biochem., physiol. and functional studies suggest that the brain renin-angiotensin system (RAS) is regulated independently of the peripheral RAS. The classical actions of **angiotensin II** in the brain include blood pressure control, drinking behavior, natriuresis and the release of vasopressin into the circulation. At least two subtypes of G-protein coupled receptors, the AT1 and the AT2 receptor, have been identified. Most of the classic actions of **angiotensin II** in the brain are mediated by AT1 receptors. The AT2 receptor is involved in brain development and neuronal regeneration and protection. Addnl., AT2 receptors can modulate some of the classic **angiotensin II** actions in the brain. Selective non-peptide AT1 receptor blockers, applied systemically, have been shown to inhibit both peripheral and brain AT1 receptors. In genetically hypertensive rats, inhibition of brain AT1 receptors may contribute to the blood pressure lowering effects of AT1 receptor blockers. Animal studies have shown that AT1 receptor antagonists enable endogenous **angiotensin II** to stimulate neuronal regeneration via activation of AT2 receptors. In animal models, inhibition of the brain RAS proved to be beneficial with respect to stroke incidence and outcome. Blockade of brain and **cerebrovascular** AT1 receptors by AT1 receptor blockers prevents the redn. in blood flow during brain ischemia, reduces the vol. of ischemic injury and improves neurol. outcome after brain ischemia. This paper reviews the actions of **angiotensin II** and its receptors in the brain, and discusses the possible consequences of AT1 receptor blockade in neuroprotection, neuroregeneration, cerebral hemodynamics and ischemia.

AB . . . functional studies suggest that the brain renin-angiotensin system (RAS) is regulated independently of the peripheral RAS. The classical actions of **angiotensin II** in the brain include blood pressure control, drinking behavior, natriuresis and the release of vasopressin into the circulation. At least. . . subtypes of G-protein coupled receptors, the AT1 and the AT2 receptor, have been identified. Most of the classic actions of **angiotensin II** in the brain are mediated by AT1 receptors. The AT2 receptor is involved in brain development and neuronal regeneration and protection. Addnl., AT2 receptors can modulate some of the classic **angiotensin II** actions in the brain. Selective non-peptide AT1 receptor blockers, applied systemically, have been shown to inhibit both peripheral and brain. . . to the blood pressure lowering effects of AT1 receptor blockers. Animal studies have shown that AT1 receptor antagonists enable endogenous **angiotensin II** to stimulate neuronal regeneration via activation of AT2 receptors. In animal models, inhibition of the brain RAS proved to be beneficial with respect to stroke incidence and outcome. Blockade of brain and **cerebrovascular** AT1 receptors by AT1 receptor blockers prevents the redn. in blood flow during brain ischemia, reduces the vol. of ischemic injury and improves neurol. outcome after brain ischemia. This paper reviews the actions of **angiotensin II** and its receptors in the brain, and discusses the possible consequences of AT1 receptor blockade in neuroprotection, neuroregeneration, cerebral hemodynamics. . .

IT Angiotensin receptor antagonists
(**angiotensin II**, AT1; renin-angiotensin system in brain and possible therapeutic implications for AT1-receptor blockers)

IT 9015-94-5, Renin, biological studies 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(renin-angiotensin system in brain and possible therapeutic implications for AT1-receptor blockers)

L1 ANSWER 13 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:551864 Document No. 138:214712 The problem of uncontrolled hypertension. Lindholm, L. H. (Department of Public Health and Clinical Medicine, Norrlands University Hospital, Umea, Swed.). Journal of Human Hypertension, 16(Suppl. 3), S3-S8 (English) 2002. CODEN: JHHYEN. ISSN: 0950-9240. Publisher: Nature Publishing Group.

AB A review. It is well established that there is a continuous relationship between raised blood pressure and the risk of cardiovascular or **cerebrovascular** disease. Both systolic and diastolic hypertension are assocd. with increased risk, but systolic blood pressure appears to be a more important determinant of risk than diastolic blood pressure. Randomized controlled trials have clearly shown that lowering blood pressure results in significant redns. in cardiovascular mortality and morbidity, and hence current hypertension management guidelines recommend target blood pressures of below 140/90 mm Hg (135/85 mm Hg in the case of the WHO/ISH guidelines). Despite the clear evidence for the benefits of antihypertensive therapy, however, blood pressure is often not adequately controlled in clin. practice. Population surveys indicate that the proportion of patients achieving even conservative blood pressure targets may be only 20% or lower. A no. of factors contribute to poor control of hypertension, including a focus by the physician on diastolic blood pressure, rather than the prognostically more important systolic pressure, and poor adherence to therapy by patients. Poor adherence may be largely attributable to adverse events, and there is evidence that the excellent tolerability profile of **angiotensin II** type 1 (AT1)-receptor blockers may help to increase the proportion of patients remaining on therapy. AT1-receptor blockers could thus make a potentially important contribution to solving the problem of uncontrolled hypertension.

AB . . . It is well established that there is a continuous relationship between raised blood pressure and the risk of cardiovascular or **cerebrovascular** disease. Both systolic and diastolic hypertension are assocd. with increased risk, but systolic blood pressure appears to be a more. . . patients. Poor adherence may be largely attributable to adverse events, and there is evidence that the excellent tolerability profile of **angiotensin II** type 1 (AT1)-receptor blockers may help to increase the proportion of patients remaining on therapy. AT1-receptor blockers could thus make. . .

IT Angiotensin receptor antagonists
(**angiotensin II**; uncontrolled hypertension problems and benefits of antihypertensive treatment in humans)

L1 ANSWER 14 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:546382 Document No. 137:118939 Ambulatory blood pressure in heart failure. Jamieson, M. J.; Jamieson, C. (Department of Pharmacology, University of Texas Health Science Center San Antonio, San Antonio, USA). Klinische Pharmakologie, 20(Digitalis Glycosides: Vascular Sites of Action), 27-37 (English) 2002. CODEN: KLPHEH. ISSN: 0937-0978. Publisher: W. Zuckschwerdt Verlag GmbH.

AB A review. Ambulatory blood pressure monitoring (ABPM) is accepted in the evaluation and management of hypertension. The use of ABPM in heart failure has received considerably less attention. Many patients with advanced heart failure experience disabling fatigue, orthostatic dizziness and symptoms of coronary and **cerebrovascular** insufficiency that may relate to periods of hypotension. These may be exacerbated by vasodilator drug therapy and may be difficult to evaluate by casual clinic recordings. ABPM in heart failure may help in: evaluating time-dependent pharmacodynamic drug effects, such as peak and end-of-dose phenomena, tolerance and rebound, (ii) titrating ACE inhibitors and other drugs to highest-tolerated doses, (iii) correlating circadian blood pressure profiles with symptoms, quality of life, severity of heart failure, progression of ventricular and renal dysfunction, risks of stroke and myocardial infarction, and life expectancy. Devices for ABPM have been beset by problems of inaccuracy and unreliability. Stds. for their manuf. and sale (including bench tests of accuracy against sphygmomanometry and intra-arterial recordings, and field tests of reliability) have been devised independently by several agencies including the British Hypertension Society (BHS) and US Assocn. for the Advancement of Medical Instrumentation (AAMI). A joint BHS/AAMI guideline is in prepn. These guidelines emphasize the suitability of ABPM devices for hypertensive patients and those under general anesthesia, and may not be applicable to ambulant individuals with heart failure and blood pressures at or below the lower end of the evaluated ranges. Prospective studies of the accuracy and reliability of ABPM devices, their clin. utility and research potential should be undertaken in patients with heart failure before their informal and uncontrolled use in this population becomes widespread.

AB . . . received considerably less attention. Many patients with advanced heart failure experience disabling fatigue, orthostatic dizziness and symptoms of coronary and **cerebrovascular** insufficiency that may relate to periods of hypotension. These may be exacerbated by vasodilator drug therapy and may be difficult. . .

IT Angiotensin receptor antagonists
(**angiotensin II**; ambulatory blood pressure in heart failure)

L1 ANSWER 15 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:540258 Document No. 137:109267 Preparation of benzoxepinopyridines as HMG-CoA reductase inhibitors. Robl, Jeffrey A.; Chen, Bang-chi; Sun, Chong-qing (USA). U.S. Pat. Appl. Publ. US 2002094977 A1 20020718, 42 pp., Cont.-in-part of U.S. Ser. No. 875,155. (English). CODEN: USXXCO. APPLICATION: US 2001-7407 20011204. PRIORITY: US 2000-PV211595 20000615; US 2001-875155 20010606.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

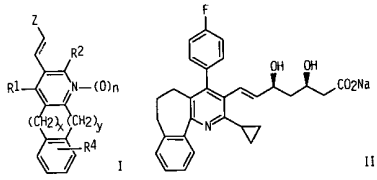
AB Title compds. I [X = O, S, SO, SO2, NR7; Z = HOCHCH2CH(OH)CH2CO2R3, 4-hydroxy-2-oxopyran-6-yl, etc.; n = 0, 1; R1, R2 = alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, cycloheteroalkyl; R3 = H, alkyl, metal ion; R4 = H, halo, CF3, etc.; R7 = H, alkyl, aryl, alkanoyl, aroyl, alkoxycarbonyl, etc.; R9, R10 = H, alkyl], were prepd. as HMG CoA reductase inhibitors active in inhibiting cholesterol biosynthesis, modulating blood serum lipids such as lowering LDL cholesterol and/or increasing HDl cholesterol, and treating hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and atherosclerosis (no data). A multistep synthesis of II is reported.

IT Angiotensin receptor antagonists
(**angiotensin II**, coadministered agents; prepn. of benzoxepinopyridines as HMG-CoA reductase inhibitors for treatment of hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, and other disorders)

IT Brain, disease
(**cerebrovascular**, treatment; prepn. of benzoxepinopyridines as HMG-CoA reductase inhibitors for treatment of hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, and other disorders)

L1 ANSWER 16 OF 123 CAPLUS COPYRIGHT 2003 ACS
2002:392237 Document No. 136:401651 Preparation of fused pyridine derivatives as HMG-CoA reductase inhibitors. Robl, Jeffrey A.; Chen, Bang-Chi; Sun, Chong-Qing (USA). U.S. Pat. Appl. Publ. US 2002061901 A1 20020523, 46 pp., Cont.-in-part of U.S. Ser. No. 875,218. (English). CODEN: USXXCO. APPLICATION: US 2001-8154 20011204. PRIORITY: US 2000-PV211594 20000615; US 2001-875218 20010606.

GI




AB The title compds. I and their pharmaceutically acceptable salts, esters, prodrug esters, and stereoisomers are claimed [wherein: Z = CH(OH)CH2CR7(OH)CH2CO2R3 or corresponding pyranone lactone derivs.; n = 0, 1; x = 0, 1, 2, 3, or 4; y = 0, 1, 2, 3 or 4, provided that at least one of x and y is other than 0; and optionally one or more carbons of (CH2)x and/or (CH2)y together with addnl. carbons form a 3 to 7 membered spirocyclic ring; R1, R2 = alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, cycloheteroalkyl; R3 = H or lower alkyl; R4 = H, halo, CF3, OH, alkyl, alkoxy, CO2H, (un)substituted NH2, cyano, (un)substituted CONH2, etc.; R7 = H, alkyl]. The compds. are HMG-CoA reductase inhibitors, and are active in inhibiting cholesterol biosynthesis and modulating blood serum lipids, for example, lowering LDL cholesterol and/or increasing HDL cholesterol (no data). I are thus useful in treating hyperlipidemia and dyslipidemia, in hormone replacement therapy, and in treating hypercholesterolemia, hypertriglyceridemia and atherosclerosis, as well as Alzheimer's disease and osteoporosis. Prepns. of several compds. are described. For instance, a multistep synthesis of fused pyridine deriv. II is reported. Compds. I may be used in a manner similar to atorvastatin, pravastatin, simvastatin, etc. Combinations of compds. I with various other drugs are claimed, the latter being specified as certain pharmacol. classes, as inhibitors of specific enzymes, as (ant)agonists of specific receptors, and as numerous named drugs.

IT Angiotensin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**angiotensin II**, therapeutic compns. also contg. antagonists of; prepn. of fused pyridine derivs. as HMG-CoA reductase inhibitors)

IT Brain, disease

L1 ANSWER 16 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
(**cerebrovascular**, treatment; prepn. of fused pyridine derivs. as HMG-CoA reductase inhibitors)

L1 ANSWER 17 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
describing the app. assembly and operation are given.

AB . . . particularly, the present invention provides an assay to detect parameters assocd. with a vascular disease including cardiovascular, stroke, pulmonary, renovascular, **cerebrovascular**, thrombotic or generalized arterial or venous condition or event including acute coronary syndrome such as but not limited to acute. . . in a coma. It is also useful in detg. the risk of a vascular disease including cardiovascular, stroke, pulmonary, renovascular, **cerebrovascular**, thrombotic or generalized arterial or venous conditions or events in a healthy subject or a subject entering into an exposure. . .

IT Angiotensin receptors
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**angiotensin II**; Immunol. diagnostic device for systemic vasculature conditions)

L1 ANSWER 17 OF 123 CAPLUS COPYRIGHT 2003 ACS

2002:220928 Document No. 136:229049 Immunological diagnostic device for systemic vasculature conditions. Christopherson, Richard Ian; Dos Remedios, Cristobal Guillermo; Celermajer, David Stephen (University of Sydney, Australia). PCT Int. Appl. WO 2002023191 A1 20020321, 89 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-AU1141 20010912. PRIORITY: AU 2000-56 20000912.

AB The invention concerns a diagnostic device including a prognostic assay for parameters which are indicative of a condition or event assocd. with the systemic vasculature. More particularly, the present invention provides an assay to detect parameters assocd. with a vascular disease including cardiovascular, stroke, pulmonary, renovascular, **cerebrovascular**, thrombotic or generalized arterial or venous condition or event including acute coronary syndrome such as but not limited to acute myocardial infarction, heart failure, atheromoma or a thrombotic condition. The identification of these parameters or more particularly a pattern of parameters enables the diagnosis of a condition or event or the detn. of the risk of development of a condition or event assocd. to the systemic vasculature. Still more particularly, the present invention is directed to a diagnostic device comprising a set of members wherein one or more of said members has or have specific or generic binding partners in a biol. sample from an animal including human subject wherein the pattern of binding of the members to the binding partners is indicative, predictive or otherwise assocd. with a likelihood of a condition or event within the systemic vasculature. The absence of detection of specific or generic binding partners is also of indicative or predictive value. This is particularly important in cases where patients are unable to communicate advice to a physician on their own condition, such as during surgery or for patients in a coma. It is also useful in detg. the risk of a vascular disease including cardiovascular, stroke, pulmonary, renovascular, **cerebrovascular**, thrombotic or generalized arterial or venous conditions or events in a healthy subject or a subject entering into an exposure to risk such as surgery or chemotherapy. The present invention is useful inter alia for the identification and/or quantitation of biochem. markers of conditions or events in the systemic vasculature such as heart disease, heart disorders, infections of the heart, stroke and thrombosis as well as the detn. of a risk of development of these conditions including the absence of disorders or absence of risk of the development of a disorder. The assessment of such conditions may be made in a clin. setting, as part of triage, as part of a routine testing protocol and/or as a lab. procedure. Diagrams

L1 ANSWER 18 OF 123 CAPLUS COPYRIGHT 2003 ACS

2002:8884 Document No. 136:209935 Vascular effects of newer cardiovascular drugs: focus on nebivolol and ACE-inhibitors. Luscher, Thomas F.; Spieker, Lukas E.; Noll, Georg; Cosentino, Francesco (Division of Cardiology, University Hospital, Zurich, CH-8091, Switz.). Journal of Cardiovascular Pharmacology, 38(Suppl. 3), S3-S11 (English) 2001. CODEN: JCPCDT. ISSN: 0160-2446. Publisher: Lippincott Williams & Wilkins.

AB A review. Alterations in the function and structure of the blood vessel wall account for most clin. events in the coronary and **cerebrovascular** circulation such as myocardial infarction and stroke. Cardiovascular drugs may exert beneficial effects on the vascular wall both at the level of the endothelium and vascular smooth muscle cells. Therefore, endothelial mediators, in particular nitric oxide (NO) and endothelin (ET), are of special interest. Drugs can modulate the expression and actions of NO, a vasodilator with antiproliferative and antithrombotic properties, and of ET, a potent vasoconstrictor and proliferative mitogenic agent. The most successful drugs in this context are statins and angiotensin-converting enzyme (ACE)-inhibitors. While statins increase the expression of NO synthase, ACE-inhibitors increase the release of NO via bradykinin-mediated mechanisms. Antioxidant properties of drugs are also important, as oxidative stress is crucial in atherosclerotic vascular disease. These properties may explain part of the effects of calcium antagonists and ACE-inhibitors. Indeed, **angiotensin II** stimulates NAD(P)H oxidases responsible for the formation of superoxide, which inactivates NO. ACE-Inhibitors thus increase the bioavailability of NO. Newer cardiovascular drugs such as nebivolol are able to directly stimulate NO release from the endothelium both in isolated arteries and in the human forearm circulation. ET receptor antagonists may exert beneficial effects in the vessel wall by preventing the effects of ET at its receptors and by reducing ET prodn. In summary, cardiovascular drugs have important effects on the vessel wall, which may be clin. relevant for the prevention and treatment of cardiovascular disease.

AB . . . Alterations in the function and structure of the blood vessel wall account for most clin. events in the coronary and **cerebrovascular** circulation such as myocardial infarction and stroke. Cardiovascular drugs may exert beneficial effects on the vascular wall both at the. . . is crucial in atherosclerotic vascular disease. These properties may explain part of the effects of calcium antagonists and ACE-inhibitors. Indeed, **angiotensin II** stimulates NAD(P)H oxidases responsible for the formation of superoxide, which inactivates NO. ACE-Inhibitors thus increase the bioavailability of NO. Newer. . .

L1 ANSWER 19 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:935406 Document No. 136:48448 Method using a rapamycin in the treatment of cardiovascular disease. Azrolan, Neal Ivan; Sehgal, Surendra Nath; Adelman, Steven Jay (American Home Products Corporation, USA). PCT Int. Appl. WO 2001097809 A2 20011227, 17 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US19179 20010614. PRIORITY: US 2000-PV212117 20000616.

AB The invention provides a method of treating or inhibiting cardiovascular, cerebral vascular, or peripheral vascular disease in a mammal in need thereof, which comprises providing the mammal an effective amt. of a rapamycin.

ST rapamycin cardiovascular **cerebrovascular** peripheral vascular disease

IT Angiotensin receptor antagonists
(**angiotensin II**; rapamycin compd. for treatment of cardiovascular disease)

IT Brain, disease
(**cerebrovascular**; rapamycin compd. for treatment of cardiovascular disease)

L1 ANSWER 20 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:868218 Document No. 136:694 Thromboxane inhibitors, compositions, and methods for therapeutic use. Saenz de Tejada, Inigo (Nitromed, Inc., USA). PCT Int. Appl. WO 2001089519 A1 20011129, 70 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US16318 20010522. PRIORITY: US 2000-PV205536 20000522.

AB The invention describes methods for treating or preventing sexual dysfunctions in males and females, and for enhancing sexual responses in males and females, by administering a therapeutically effective amt. of at least one thromboxane inhibitor, and, optionally, at least one compd. that donates, transfers, or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, and/or at least one vasoactive agent. The male or female may preferably be diabetic. The invention also provides compns. comprising at least one thromboxane inhibitor, and, at least one compd. that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, and, optionally, at least one therapeutic agent, such as, vasoactive agents, nonsteroidal antiinflammatory compd. (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, anticoagulants, angiotensin converting enzymes (ACE) inhibitors, **angiotensin II** receptor antagonists, renin inhibitors, and mixts. thereof. The invention further provides methods for treating or preventing ischemic heart disorders, myocardial infarction, angina pectoris, stroke, migraine, **cerebral hemorrhage**, cardiac fatalities, **transient ischemic attacks**, complications following organ transplants, coronary artery bypasses, angioplasty, endarterectomy, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shock of various organs, nephritis, graft rejection, cancerous metastases, pregnancy-induced hypertension, preeclampsia, eclampsia, thrombotic and thromboembolic disorders, intrauterine growth, gastrointestinal disorders, renal diseases and disorders, disorders resulting from elevated uric acid levels, and dysmenorrhea, and for inhibiting platelet aggregation or platelet adhesion or relaxing smooth muscles. The compds. and/or compns. of the present invention can also be provided in the form of a pharmaceutical kit.

AB . . . therapeutic agent, such as, vasoactive agents, nonsteroidal antiinflammatory compd. (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, anticoagulants, angiotensin converting enzymes (ACE) inhibitors, **angiotensin II** receptor antagonists, renin

L1 ANSWER 20 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
inhibitors, and mixts. thereof. The invention further provides methods for treating or preventing ischemic heart disorders, myocardial infarction, angina pectoris, stroke, migraine, **cerebral hemorrhage**, cardiac fatalities, **transient ischemic attacks**, complications following organ transplants, coronary artery bypasses, angioplasty, endarterectomy, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shock of various. . .

IT Angiotensin receptor antagonists
(**angiotensin II**; thromboxane inhibitors, compns., and methods for therapeutic use)

L1 ANSWER 21 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:824362 Document No. 137:41454 Pre-treatment with candesartan protects from cerebral ischaemia. Ito, Takeshi; Nishimura, Yasuaki; Saavedra, Juan (Section on Pharmacology, NIMH, NIH, Bethesda, MD, 20892, USA). JRAAS, 2(3), 174-179 (English) 2001. CODEN: JRAAAG. ISSN: 1470-3203. Publisher: JRAAS Ltd..

AB **Angiotensin II** (Ang II) regulates cerebral blood flow by stimulating cerebral vasoconstriction via AT1- receptors. In adult spontaneously hypertensive rats (SHR), the **cerebrovascular** autoregulatory curve is shifted to the right, in the direction of higher blood pressures, an indication of excessive **cerebrovascular** vasoconstriction. A restricted capacity to dilate cerebral blood vessels may be responsible for the enhanced vulnerability to **cerebrovascular** ischemia during hypertension. We found that chronic treatment with the AT1-receptor antagonist, candesartan, (0.5 mg/kg/day for 14 days, via osmotic minipumps implanted in the s.c. tissue) blocked Ang II binding to AT1-receptors in cerebral blood vessels and in brain areas involved in the regulation of **cerebrovascular** flow, and increased the ratio of lumen-wall area in the middle cerebral artery. Candesartan treatment normalized the lower part of the autoregulatory curve in SHR, and markedly decreased cerebral ischemia as a consequence of middle cerebral artery occlusion with reperfusion. Protection from ischemia is related to arterial remodelling, enhanced compensatory vasodilatation in the peripheral area of ischemia, decreased redn. in cerebral blood flow following the occlusion of a major cerebral blood vessel, and protection from injury in the periphery of the lesion. Our results indicate that pre-treatment with AT1-antagonists such as candesartan could be of benefit in the prevention and treatment of brain ischemia.

AB **Angiotensin II** (Ang II) regulates cerebral blood flow by stimulating cerebral vasoconstriction via AT1- receptors. In adult spontaneously hypertensive rats (SHR), the **cerebrovascular** autoregulatory curve is shifted to the right, in the direction of higher blood pressures, an indication of excessive **cerebrovascular** vasoconstriction. A restricted capacity to dilate cerebral blood vessels may be responsible for the enhanced vulnerability to **cerebrovascular** ischemia during hypertension. We found that chronic treatment with the AT1-receptor antagonist, candesartan, (0.5 mg/kg/day for 14 days, via osmotic. . . tissue) blocked Ang II binding to AT1-receptors in cerebral blood vessels and in brain areas involved in the regulation of **cerebrovascular** flow, and increased the ratio of lumen-wall area in the middle cerebral artery. Candesartan treatment normalized the lower part of. . .

IT Angiotensin receptor antagonists
(**angiotensin II**; pre-treatment with candesartan protects from cerebral ischemia)

L1 ANSWER 22 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:710805 Document No. 136:353152 Genetic risk factors for **cerebral infarction**. Tamura, Mitsuru; Ito, Daisuke (School of Medicine, Keio University, Japan). Molecular Medicine (Tokyo, Japan), 38(Rinji Zokango, Seikatsu Shykanbyo), 364-369 (Japanese) 2001. CODEN: MOLMEL. ISSN: 0918-6557. Publisher: Nakayama Shoten.

AB A review, on the title topic, discussing genetic risk factors in atherosclerosis and thrombotic disorders; atherosclerosis- and hypertension-assocd. factors (e.g. apolipoprotein E, apolipoprotein LP(a), angiotensin-converting enzyme and **angiotensin II** receptors, NO synthase, methylenetetrahydrofolate reductase, paraoxonase, CD antigens, etc); and factors in assocn. with thrombotic disorders (blood-coagulation factors, prototrombin, thrombomodulin; fibrinogen, etc).

TI Genetic risk factors for **cerebral infarction**

AB . . . genetic risk factors in atherosclerosis and thrombotic disorders; atherosclerosis- and hypertension-assocd. factors (e.g. apolipoprotein E, apolipoprotein LP(a), angiotensin-converting enzyme and **angiotensin II** receptors, NO synthase, methylenetetrahydrofolate reductase, paraoxonase, CD antigens, etc); and factors in assocn. with thrombotic disorders (blood-coagulation factors, prototrombin, thrombomodulin;. . .

ST review genetic risk factor **cerebral infarction**

IT Atherosclerosis
Thrombosis
(genetic risk factors for **cerebral infarction**)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(genetic risk factors for **cerebral infarction**)

IT Diagnosis
(genetic; genetic risk factors for **cerebral infarction**)

IT Brain, disease
(infarction; genetic risk factors for **cerebral infarction**)

L1 ANSWER 23 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT Renin-angiotensin system
(renin-angiotensin system on cerebral perfusion following **subarachnoid hemorrhage**)

IT Meninges
(**subarachnoid hemorrhage**; renin-angiotensin system on cerebral perfusion following **subarachnoid hemorrhage**)

IT Nervous system
(sympathetic; renin-angiotensin system on cerebral perfusion following **subarachnoid hemorrhage**)

IT Angiotensin receptors
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(type AT1; renin-angiotensin system on cerebral perfusion following **subarachnoid hemorrhage**)

IT 51-41-2, Noradrenaline 11128-99-7, **Angiotensin-II**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(renin-angiotensin system on cerebral perfusion following **subarachnoid hemorrhage**)

IT 9015-94-5, Renin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(renin-angiotensin system on cerebral perfusion following **subarachnoid hemorrhage**)

L1 ANSWER 23 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:695120 Document No. 136:3888 Impact of the renin-angiotensin system on cerebral perfusion following **subarachnoid hemorrhage** in the rat. Fassot, Celine; Lambert, Gavin; Elghozi, Jean-Luc; Lambert, Elisabeth (INSERM E 0107, Faculte de Medecine, Paris, 75270, Fr.). Journal of Physiology (Cambridge, United Kingdom), 535(2), 533-540 (English) 2001. CODEN: JPHYA7. ISSN: 0022-3751. Publisher: Cambridge University Press.

AB 1. This study investigated the effects of blocking the AT1 angiotensin receptors with irbesartan, either peripherally or centrally, on systemic blood pressure, intracranial pressure and cerebral perfusion pressure following exptl. **subarachnoid hemorrhage** (SAH) in urethane-anasthetized rats. Sympathetic nervous activation was detd. by measuring plasma noradrenaline levels. 2. In untreated animals, SAH induced a sustained increased in intracranial pressure from 2.1.+-.0.3 to 16.+-.2 mm Hg (3 h, P < 0.001). Cerebral perfusion pressure was reduced by 20% (P < 0.001), this redn. being maintained for 3 h. Sympathetic activation was evident in the high level of plasma noradrenaline measured 3 h post-SAH (751.+-.104 vs. 405.+-.33 pg ml-1, P < 0.05). 3. Acute peripheral pretreatment with irbesartan (3 mg kg-1, I.V.) prevented the rise in plasma noradrenaline and further aggravated the decrease in cerebral perfusion pressure by producing transient systemic hypotension (blood pressure was 85.+-.6 mmHg at 2 h post-SAH vs. 100.+-.3 mmHg, P < 0.01). 4. Intracisternal pretreatment with irbesartan (0.035 mg) did not prevent the rise in plasma noradrenaline post-SAH but enhanced the rise in intracranial pressure by 75% compared with untreated animals. 5. This study demonstrates that peripheral endogenous **angiotensin II** interacts with the sympathetic nervous system in order to maintain an adequate cerebral perfusion following SAH. Endogenous **angiotensin II** in the brain seems to exert a protective effect by counteracting the elevation in intracranial pressure that occurs following exptl. SAH.

TI Impact of the renin-angiotensin system on cerebral perfusion following **subarachnoid hemorrhage** in the rat

AB . . . angiotensin receptors with irbesartan, either peripherally or centrally, on systemic blood pressure, intracranial pressure and cerebral perfusion pressure following exptl. **subarachnoid hemorrhage** (SAH) in urethane-anasthetized rats. Sympathetic nervous activation was detd. by measuring plasma noradrenaline levels. 2. In untreated animals, SAH induced. . . but enhanced the rise in intracranial pressure by 75% compared with untreated animals. 5. This study demonstrates that peripheral endogenous **angiotensin II** interacts with the sympathetic nervous system in order to maintain an adequate cerebral perfusion following SAH. Endogenous **angiotensin II** in the brain seems to exert a protective effect by counteracting the elevation in intracranial pressure that occurs following exptl.. . .

ST renin angiotensin system brain **subarachnoid hemorrhage**

L1 ANSWER 24 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:672361 Document No. 136:214735 Relation between the renin-angiotensin gene system and endothelial NO synthase gene polymorphism and angiocomplications of type 2 diabetes mellitus. Sergeeva, T. V.; Chistyakov, D. A.; Kobalova, Zh. D.; Moiseev, V. S. (Kafedra Vnutrennikh Boleznei, Ross. Univ. Druzhby Narodov, Moscow, Russia). Problemy Endokrinologii, 47(4), 18-23 (Russian) 2001. CODEN: PROEAS. ISSN: 0375-9660. Publisher: Izdatel'stvo Meditsina.

AB The insertion/deletion (I/D) polymorphism of angiotensin 1-converting enzyme (ACE) gene, T174M (threonine substitution for methionine in position 174 of amino acid sequence) polymorphism of angiotensinogen (AGT) gene, A1166C polymorphism of **angiotensin II** vascular (type 1) receptor (ATIR) gene, and ecNOS4a/4b polymorphisms of endothelial NO synthase (NOS3) gene were studied by the polymerase chain reaction (PCR) in patients with type 2 diabetes mellitus and arterial hypertension uncomplicated (control, n = 52) and complicated with cardiovascular diseases (myocardial infarction, n = 53, and acute **cerebrovascular** disorders, n = 50). Protective effect of I/I genotype on development of myocardial infarction in diabetics was shown. The absence of significant differences in the distribution of alleles and genotypes of AGT gene in three groups of patients indicates that this gene is hardly involved in the formation of cardiovascular complications in type 2 diabetes. A strong assocn. between A1166 C polymorphism of AZT1R gene and development of myocardial infarction in patients with type 2 diabetes and essential hypertension of the Moscow population was revealed; allele A and genotype AA attenuate the risk of early myocardial infarction, while allele C and genotype CC enhance it. A relationship between mini satellite ecNOS4a/4b polymorphism of NOS3 gene cardiovascular diseases was detected in patients with type 2 diabetes and essential hypertension. Allele 4a and genotypes 4a/4b and 4a/4a are pronounced risk markers, and allele 4b and genotype 4b/4b carrier ship is assocd. with a low risk of this complication.

AB . . . T174M (threonine substitution for methionine in position 174 of amino acid sequence) polymorphism of angiotensinogen (AGT) gene, A1166C polymorphism of **angiotensin II** vascular (type 1) receptor (ATIR) gene, and ecNOS4a/4b polymorphisms of endothelial NO synthase (NOS3) gene were studied by the polymerase. . . and arterial hypertension uncomplicated (control, n = 52) and complicated with cardiovascular diseases (myocardial infarction, n = 53, and acute **cerebrovascular** disorders, n = 50). Protective effect of I/I genotype on development of myocardial infarction in diabetics was shown. The absence. . .

IT Brain, disease
(**cerebrovascular**; renin-angiotensin gene system and endothelial nitric oxide synthase gene polymorphism and angiocomplications of NIDDM)

L1 ANSWER 25 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:540627 Document No. 135:165387 Diabetic macroangiopathy and genetic polymorphisms in Japanese patients with type 2 diabetes. Muto, Kazuko; Uchigata, Yasuko; Honda, Masashi; Otani, Toshika; Iwamoto, Yasuhiko (Dep. Med. III, Diabetes Cent., Tokyo Women's Med. Univ. Sch. Med., Japan). Tokyo Joshi Ika Daigaku Zasshi, 71(5.6), 319-330 (Japanese) 2001. CODEN: TJIZAF. ISSN: 0040-9022. Publisher: Tokyo Joshi Ika Daigaku Gakkai.

AB The main cause of mortality in type 2 diabetic patients is macroangiopathy including coronary heart disease (CHD), **cerebrovascular** disease (CVD), and obstructive atherosclerosis (ASO). Recent genetic studies showed that these vascular diseases in non-diabetic patients were largely assocd. with certain genetic polymorphisms. We therefore investigated the relationship between macroangiopathy and the genetic polymorphisms in Japanese patients with type 2 diabetes by a case-control study. A total of 157 patients with type 2 diabetes were divided into 81 with either CHD, CVD or ASO (pos. group) and 76 without all (neg. group). Two groups were matched with age, duration, HbA1c and lipid metab. Healthy individuals who had no abnormality of glucose and lipid metabs. served as controls. The gene polymorphisms used in this study were as follows: the deletion/insertion allele of angiotensin-converting enzyme (ACE) gene, 1166A/C allele of **angiotensin II** type I receptor (AT1R) gene, PIA1/PIA2 allele of platelet glycoprotein IIIa receptor (GPIIIa) gene, TaqIB and Int14G/A allele of cholesteryl ester transfer protein (cETP), 188Gly/Glu allele of lipoprotein lipase (LPL) gene, 4a/b allele of endothelial nitric oxide synthase (eNOS) gene, 192Gln/Arg allele of paraoxonase (PON) gene, and 677C/T allele of methylenetetrahydrofolate reductase (MTHFR) gene. These gene polymorphisms in healthy control were on the way to Hardy-Weinberg equil. The result showed that there was no statistical difference in the polymorphisms between the pos. and neg. groups. It suggests that the development of macroangiopathy in type 2 diabetes was not assocd. these gene polymorphisms.

AB The main cause of mortality in type 2 diabetic patients is macroangiopathy including coronary heart disease (CHD), **cerebrovascular** disease (CVD), and obstructive atherosclerosis (ASO). Recent genetic studies showed that these vascular diseases in non-diabetic patients were largely assocd.. . . gene polymorphisms used in this study were as follows: the deletion/insertion allele of angiotensin-converting enzyme (ACE) gene, 1166A/C allele of **angiotensin II** type I receptor (AT1R) gene, PIA1/PIA2 allele of platelet glycoprotein IIIa receptor (GPIIIa) gene, TaqIB and Int14G/A allele of cholesteryl. . .

IT Brain, disease
(**cerebrovascular**; diabetic macroangiopathy and genetic polymorphisms in Japanese patients with type 2 diabetes)

L1 ANSWER 26 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:467861 Document No. 136:303865 The **angiotensin II** receptor antagonist candesartan cilexetil (TCV-116) ameliorates retinal disorders in rats. Nagisa, Y.; Shintani, A.; Nakagawa, S. (Pharmaceutical Research Division, Pharmacology Research Laboratories II, Takeda Chemical Industries, Osaka, Japan). Diabetologia, 44(7), 883-888 (English) 2001. CODEN: DBTGAJ. ISSN: 0012-186X. Publisher: Springer-Verlag.

AB The results of the EUCLID trial (EURODIAB Controlled Trial of Lisinopril in Insulin-dependent Diabetes Mellitus) highlighted the importance of the renin-angiotensin system in the pathogenesis of diabetic retinopathy. Candesartan cilexetil (TCV-116), a potent **angiotensin II** (**AII**) receptor antagonist, has beneficial effects on hypertension as well as on heart, renal, and **cerebrovascular** disease. The authors aimed to evaluate the effectiveness of candesartan cilexetil in ameliorating retinal disorders induced by hyperglycemia. Methods. The authors compared retinal vascular endothelial growth factor (VEGF) mRNA expression and the latencies of retinal oscillatory potentials in TCV-116-treated and control groups of stroke-prone spontaneously hypertensive rats with streptozocin (STZ)-induced diabetes. Results. Retinal VEGF mRNA expression was significantly higher and the latencies of oscillatory potentials were significantly elongated in STZ-treated spontaneously hypertensive rats compared with a non-treated spontaneously hypertensive rat group matched for age. These changes were dependent on hyperglycemia but independent of hypertension. Treatment with TCV-116 (3 mg/kg) significantly diminished retinal VEGF mRNA expression and the latencies of oscillatory potential peaks, but had no effect on plasma glucose concns. These results suggest that TCV-116 is effective in preventing the development of diabetic retinopathy already in the early stages.

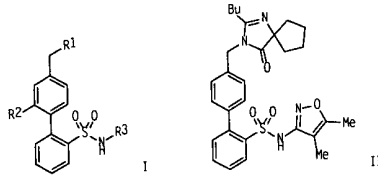
TI The **angiotensin** II receptor antagonist candesartan cilexetil (TCV-116) ameliorates retinal disorders in rats

AB . . . Diabetes Mellitus) highlighted the importance of the renin-angiotensin system in the pathogenesis of diabetic retinopathy. Candesartan cilexetil (TCV-116), a potent **angiotensin II** (**AII**) receptor antagonist, has beneficial effects on hypertension as well as on heart, renal, and **cerebrovascular** disease. The authors aimed to evaluate the effectiveness of candesartan cilexetil in ameliorating retinal disorders induced by hyperglycemia. Methods. The. . .

IT Angiotensin receptor antagonists
(**angiotensin II**; candesartan cilexetil (TCV-116) ameliorates retinal disorders in rats)

L1 ANSWER 27 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:453059 Document No. 135:46172 Preparation of N-isoxazolyl biphenylsulfonamides and related compounds as dual **angiotensin II** and endothelin receptor antagonists.. Murugesan, Natesan; Tellew, John E.; Macor, John E.; Gu, Zhengxiang (Bristol-Myers Squibb Co., USA). PCT Int. Appl. WO 2001044239 A2 20010621, 287 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US33730 20001213. PRIORITY: US 1999-464037 19991215; US 2000-481197 20000111; US 2000-513779 20000225; US 2000-604322 20000626; US 2000-643640 20000822.

GI




I II

AB Title compds. (I; R1 = specified oxoimidazolyl, pyridoimidazolyl, pyridylamino, triazolyl, quinolinyloxy, etc.; R2 = H, halo, CHO, (halo)alkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxy, cyano, OH, NO2, etc.; R3 = heteroaryl; with provisos) were prepd. as dual **angiotensin II** and endothelin receptor antagonists for treatment of hypertension and other diseases (no data). Thus, 4-BrC6H4CH2OH was coupled with [2-[[(4,5-dimethyl-3-isoxazolyl)[(2-methoxyethoxy)methyl]amino]sulfonyl]phenyl]boronic acid to give N-(4,5-dimethyl-3-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide (66%). This was brominated to give the 4'-bromomethyl deriv. (90%), reacted with 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride, and deprotected (49% for two steps) to give II.

TI Preparation of N-isoxazolyl biphenylsulfonamides and related compounds as dual **angiotensin II** and endothelin receptor antagonists.

AB . . . CHO, (halo)alkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxy, cyano, OH, NO2, etc.; R3 = heteroaryl; with provisos) were prepd. as dual **angiotensin II** and endothelin receptor

L1 ANSWER 27 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
antagonists for treatment of hypertension and other diseases (no data). Thus, 4-BrC6H4CH2OH was coupled with [2-[[(4,5-dimethyl-3-isoxazolyl)[(2-methoxyethoxy)methyl]amino]sulfonyl]phenyl]boronic acid. . .

IT Angiotensin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(**angiotensin II**, antagonists; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Endothelin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(antagonists; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Prostate gland
(benign hyperplasia, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Sexual behavior
(disorder, treatment of female; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Heart, disease
Kidney, disease
(failure, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Sexual behavior
(impotence, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Antiarteriosclerotics
Antiasthmatics
Antihypertensives
Antimigraine agents
Antitumor agents
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Growth inhibitors, animal
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Artery, disease
(restenosis, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

L1 ANSWER 27 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT Meninges
(**subarachnoid hemorrhage**, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Endotoxemia
Ischemia
(treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

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L1 ANSWER 27 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

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L1 ANSWER 27 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT 56-12-2, 4-Aminobutyric acid, reactions 75-03-6, Iodoethane 78-09-1, Tetraethyl orthocarbonate 79-03-8, Propionyl chloride 79-44-7, Dimethylcarbamyl chloride 95-89-6, 2-Chloro-3,6-dimethylpyrazine 109-81-9, N-Methylethylenediamine 124-40-3, Dimethylamine, reactions 127-08-2, Potassium acetate 541-41-3, Ethyl chloroformate 543-27-1, Isobutyl chloroformate 589-15-1, 4-Bromobenzyl bromide 627-03-2, Ethoxyacetic acid 638-29-9, Valeryl chloride 676-58-4, Methylmagnesium

L1 ANSWER 27 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

chloride 680-15-9 767-00-0, 4-Cyanophenol 865-33-8, Potassium methoxide 873-75-6, 4-Bromobenzyl alcohol 1117-97-1, N-Methoxy-N-methylamine 1122-91-4, 4-Bromobenzaldehyde 1450-75-5 1530-32-1, Ethyltriphenylphosphonium bromide 1609-86-5, tert-Butyl isocyanate 2835-98-5 2905-25-1, 2-Bromobenzenesulfonyl chloride 3959-07-7, 4-Bromobenzylamine 4858-85-9, 2,3-Dichloropyrazine 5326-34-1, 4-Bromo-3-nitrotoluene 6228-47-3, Propyltriphenylphosphonium bromide 6482-24-2, 1-Bromo-2-methoxyethane 13734-41-3 14508-49-7, 2-Chloropyrazine 14678-02-5, 5-Amino-3-methylisoxazole 22059-22-9, Acetamide oxime 22884-29-3, Isobutyltriphenylphosphonium bromide 28466-21-9, 4-Amino-1,3,5-trimethylpyrazole 29006-02-8 33670-32-5, Methoxymethyltriphenylphosphonium bromide 34328-47-7 34841-06-0, 3-Bromo-4-methoxybenzaldehyde 40155-28-0, 2-Chloro-3-methoxypyrazine 41963-20-6, 4-Bromo-3-methylbenzonitrile 53553-14-3, Methyl 2-chloro-3-nitrobenzoate 53596-60-4 60421-23-0 74410-26-7 76513-69-4, 2-(Trimethylsilyl)ethoxymethyl chloride 78775-11-8 87199-17-5, 4-Formylphenylboronic acid 89464-87-9, 2-Amino-3-methoxy-5-methylpyrazine 98946-18-0, tert-Butyl 2,2,2-trichloroacetimidate 109072-25-5 120077-69-2 124750-49-8 125110-82-9, 4,4-Difluoropentanoic acid 133059-43-5 133240-06-9 138402-05-8 148547-19-7, Methyl 4-bromo-3-methylbenzoate 150691-04-6 151257-01-1 153039-15-7 160313-50-8 162647-41-8 167985-34-4 176961-13-0 195436-86-3 254746-77-5 254746-78-6 254746-79-7 254746-80-0 254746-81-1

RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT 14847-51-9P 79047-47-5P 89003-95-2P 123652-98-2P 142031-67-2P
160313-48-4P 176961-30-1P 189762-06-9P 189762-08-1P 190197-86-5P
254744-14-4P 254744-15-5P 254744-16-6P 254744-17-7P 254744-18-8P
254744-19-9P 254744-20-2P 254744-21-3P 254744-22-4P 254744-23-5P
254744-24-6P 254744-25-7P 254744-26-8P 254744-27-9P 254744-28-0P
254744-29-1P 254744-30-4P 254744-31-5P 254744-32-6P 254744-33-7P
254744-34-8P 254744-35-9P 254744-36-0P 254744-37-1P 254744-38-2P
254744-39-3P 254744-40-6P 254744-41-7P 254744-42-8P 254744-43-9P
254744-44-0P 254744-45-1P 254744-46-2P 254744-47-3P 254744-48-4P
254744-49-5P 254744-50-8P 254744-51-9P 254744-52-0P 254744-53-1P
254744-54-2P 254744-55-3P 254744-56-4P 254744-58-6P 254744-60-0P
254744-63-3P 254744-65-5P 254744-68-8P 254744-70-2P 254744-73-5P
254744-78-0P 254744-81-5P 254744-84-8P 254744-86-0P 254744-87-1P
254744-90-6P 254744-91-7P 254744-95-1P 254744-98-4P 254745-00-1P
254745-03-4P 254745-06-7P 254745-08-9P 254745-12-5P 254745-14-7P
254745-19-2P 254745-23-8P 254745-28-3P 254745-31-8P 254745-36-3P
254745-39-6P 254745-42-1P 254745-43-2P 254745-45-4P 254745-46-5P
254745-48-7P 254745-49-8P 254745-50-1P 254745-51-2P 254745-52-3P
254745-53-4P 254745-54-5P 254745-55-6P 254745-57-8P 254745-58-9P
254745-60-3P 254745-61-4P 254745-62-5P 254745-64-7P 254745-66-9P
254745-68-1P 254745-70-5P 254745-72-7P 254745-73-8P 254745-76-1P
254745-77-2P 254745-78-3P 254745-79-4P 254745-80-7P 254745-81-8P
254745-82-9P 254745-83-0P 254745-84-1P 254745-85-2P 254745-86-3P

L1 ANSWER 27 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

254745-87-4P 254745-88-5P 254745-89-6P 254745-90-9P 254745-91-0P
254745-92-1P 254745-93-2P 254745-94-3P 254745-95-4P 254745-96-5P
254745-97-6P 254745-98-7P 254745-99-8P 254746-00-4P 254746-01-5P
254746-03-7P 254746-04-8P 254746-06-0P 254746-07-1P 254746-08-2P
254746-09-3P 254746-10-6P 254746-11-7P 254746-12-8P 254746-13-9P
254746-14-0P 254746-15-1P 254746-16-2P 254746-18-4P 254746-19-5P
254746-20-8P 254746-21-9P 254746-22-0P 254746-23-1P 254746-24-2P
254746-25-3P 254746-26-4P 254746-27-5P 254746-28-6P 254746-29-7P
254746-30-0P 254746-31-1P 254746-32-2P 254746-33-3P 254746-34-4P
254746-35-5P 254746-36-6P 254746-37-7P 254746-38-8P 254746-39-9P
254746-40-2P 254746-41-3P 254746-42-4P 254746-43-5P 254746-44-6P
254746-45-7P 254746-46-8P 254746-47-9P 254746-48-0P 254746-49-1P
254746-50-4P 254746-51-5P 254746-52-6P 254746-53-7P 254746-54-8P
254746-55-9P 254746-56-0P 254746-57-1P 254746-58-2P 254746-59-3P
254746-60-6P 254746-61-7P 254746-62-8P 254746-63-9P 254746-64-0P
254746-65-1P 254746-66-2P 254746-67-3P 254746-68-4P 254746-69-5P
254746-70-8P 254746-71-9P 254746-72-0P 254746-73-1P 254746-74-2P
254746-75-3P 254746-76-4P 254746-82-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

L1 ANSWER 28 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

Renin-angiotensin system

(renin-angiotensin and vasopressin systems in acute and chronic alterations in blood pressure variability following exptl. **subarachnoid hemorrhage**)

IT Vasopressin receptors

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(renin-angiotensin and vasopressin systems in acute and chronic alterations in blood pressure variability following exptl. **subarachnoid hemorrhage**)

IT Meninges

(**subarachnoid hemorrhage**; renin-angiotensin and vasopressin systems in acute and chronic alterations in blood pressure variability following exptl. **subarachnoid hemorrhage**)

IT 11000-17-2, Vasopressin 11128-99-7, **angiotensin II**

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(renin-angiotensin and vasopressin systems in acute and chronic alterations in blood pressure variability following exptl. **subarachnoid hemorrhage**)

L1 ANSWER 28 OF 123 CAPLUS COPYRIGHT 2003 ACS

2001:207388 Document No. 135:75027 Acute and chronic alterations in blood pressure variability following experimental subarachnoid haemorrhage. Fassot, C.; Lambert, E.; Lambert, G.; Friberg, P.; Elghozi, J.-L. (INSERM E0107, Biomecanique et Pharmacologie de la Paroi Arterielle, Paris, 75670, Fr.). Regulatory Peptides, 99(1), 31-39 (English) 2001. CODEN: REPPDY. ISSN: 0167-0115. Publisher: Elsevier Science Ireland Ltd..

AB This study examd. the role of the renin-angiotensin and vasopressin systems on systolic blood pressure (SBP) variability following **subarachnoid hemorrhage** (SAH) in conscious rats. Animals received no treatment, the **angiotensin II** AT1 receptor antagonist, losartan, or the vascular vasopressin receptor antagonist, AVPX. SAH resulted in a transient sympathetic activation as estd. from the increase in the mid-frequency oscillations of SBP (3.2 mm Hg2, 3 h after the injury vs. 1.3 mm Hg2 in control conditions). On the second and fourth day following SAH, a marked elevation in the low-frequency component of SBP was obsd. (7.1 mm Hg2 on day 2 vs. 2.6 mm Hg2 in control conditions, and 6.3 mm Hg2 on day 4 vs. 2.6 mm Hg2 in control conditions). Pre-treatment with losartan prevented the acute rise in the mid-frequency oscillations in SBP and partially reduced the low-frequency component obsd. at 2 and 4 days. Administration of AVPX on the second and fourth day following SAH normalized the elevated low-frequency oscillations in SBP. This study indicates that the modifications in SBP variability obsd. in the early and delayed stage after **subarachnoid hemorrhage** involve **angiotensin II**. Vasopressin seems to be implicated in the delayed development of low-frequency fluctuations of SBP.

AB This study examd. the role of the renin-angiotensin and vasopressin systems on systolic blood pressure (SBP) variability following **subarachnoid hemorrhage** (SAH) in conscious rats. Animals received no treatment, the **angiotensin II** AT1 receptor antagonist, losartan, or the vascular vasopressin receptor antagonist, AVPX. SAH resulted in a transient sympathetic activation as estd.. . . oscillations in SBP. This study indicates that the modifications in SBP variability obsd. in the early and delayed stage after **subarachnoid hemorrhage** involve **angiotensin II**. Vasopressin seems to be implicated in the delayed development of low-frequency fluctuations of SBP.

ST **subarachnoid hemorrhage** blood pressure alteration angiotensin vasopressin

IT Angiotensin receptors

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(AT1; renin-angiotensin and vasopressin systems in acute and chronic alterations in blood pressure variability following exptl. **subarachnoid hemorrhage**)

IT Blood pressure

L1 ANSWER 29 OF 123 CAPLUS COPYRIGHT 2003 ACS

2001:136306 Document No. 135:90868 Renin-angiotensin system gene polymorphisms, blood pressure, dyslipidemia, and diabetes in Hong Kong Chinese: A significant association of the ACE insertion/deletion polymorphism with type 2 diabetes. Thomas, G. Neil; Tomlinson, Brian; Chan, Juliana C. N.; Sanderson, John E.; Cockram, Clive S.; Critchley, Julian A. J. H. (Division of Clinical Pharmacology, Department of Medicine and Therapeutics, The Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Peop. Rep. China). Diabetes Care, 24(2), 356-361 (English) 2001. CODEN: DICAD2. ISSN: 0149-5992. Publisher: American Diabetes Association, Inc..

AB In Chinese populations, hypertension is common and is a major risk factor for **cerebrovascular** and coronary heart disease, particularly when assocd. with diabetes. The clustering of these disorders and dyslipidemia and obesity is termed the metabolic syndrome and is increasing in prevalence in the populations of modernizing Asian nations. The renin-angiotensin system (RAS) helps maintain blood pressure and salt homeostasis and may play a role in the pathogenesis of aspects of the metabolic syndrome. We investigated three RAS gene polymorphisms-the ACE insertion/deletion (I/D), angiotensinogen (AGT) M235T, and **angiotensin II** type 1 receptor (AT1R) A1166C polymorphisms-for a possible role in modulating these disorders in 853 Chinese subjects with varying components of the metabolic syndrome. The three gene polymorphisms of this cross-sectional study were detected using polymerase chain reaction-based protocols. The genotype frequencies were compared between the controls (n = 119) and both overlapping and nonoverlapping groups of patients with type 2 diabetes, hypertension, and dyslipidemia using .chi.2 test. Differences in levels of the biochem. parameters between the genotypes were detd. using anal. of variance. No significant relationship was identified between these polymorphisms and blood pressure in this population. Although the AT1RA1166C polymorphism was not assocd. with any aspect of the metabolic syndrome examd., there was limited evidence to suggest that the AGT M235T polymorphism may be assocd. with cholesterol levels. The ACE I allele was significantly more frequent in each group comprising subjects with type 2 diabetes/glucose intolerance (GIT), and the I allele was assocd. with higher fasting plasma glucose levels. These findings suggest that these polymorphisms are unlikely to be involved in the pathogenesis of hypertension. The ACE I/D polymorphism was assocd. with the metabolic syndrome, having a higher frequency of I allele-contg. genotypes in those groups, but this appeared to result predominantly from the relationship with type 2 diabetes/GIT in this population of Chinese subjects.

AB In Chinese populations, hypertension is common and is a major risk factor for **cerebrovascular** and coronary heart disease, particularly when assocd. with diabetes. The clustering of these disorders and dyslipidemia and obesity is termed. . . pathogenesis of aspects of the metabolic syndrome. We investigated three RAS gene polymorphisms-the ACE insertion/deletion (I/D), angiotensinogen (AGT) M235T, and **angiotensin II** type 1 receptor (AT1R) A1166C polymorphisms-for a possible role in modulating these disorders in 853 Chinese subjects with varying components. . .

L1 ANSWER 29 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

L1 ANSWER 30 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
(antagonists; preventives for recurrence of **cerebrovascular** failure contg. benzimidazoles as **angiotensin II** antagonists)
IT 114798-26-4, Losartan 133040-01-4, Eprosartan 137862-53-4, Valsartan 138402-11-6, Irbesartan 139481-59-7, Candesartan 144689-63-4, Olmesartan 144701-48-4, Telmisartan 145040-37-5, Candesartan cilexetil 145733-36-4, Tasosartan 147403-03-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preventives for recurrence of **cerebrovascular** failure contg. benzimidazoles as **angiotensin II** antagonists)

L1 ANSWER 30 OF 123 CAPLUS COPYRIGHT 2003 ACS
2001:63850 Document No. 134:120961 Preventives for recurrence of **cerebrovascular** failure and agents for ameliorating troubles following **cerebrovascular** failure and inhibiting progress thereof. Ojima, Mami; Kitayoshi, Takahito; Miyamoto, Masaomi (Takeda Chemical Industries, Ltd., Japan). PCT Int. Appl. WO 2001005428 A1 20010125, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2000-JP4830 20000719. PRIORITY: JP 1999-205877 19990721.
AB Disclosed are benzmidazole derivs. as preventives for the recurrence of **cerebrovascular** failure and agents for ameliorating troubles following **cerebrovascular** failure and inhibiting the progress thereof which contain compds. having an antagonism to **angiotensin II**, prodrugs thereof or salts of the same. For example, a capsule contg. candesartan cilexetil 30, lactose 90, microcryst. cellulose 70, and magnesium stearate 10 mg can be formulated.
TI Preventives for recurrence of **cerebrovascular** failure and agents for ameliorating troubles following **cerebrovascular** failure and inhibiting progress thereof
AB Disclosed are benzmidazole derivs. as preventives for the recurrence of **cerebrovascular** failure and agents for ameliorating troubles following **cerebrovascular** failure and inhibiting the progress thereof which contain compds. having an antagonism to **angiotensin II**, prodrugs thereof or salts of the same. For example, a capsule contg. candesartan cilexetil 30, lactose 90, microcryst. cellulose 70, . .
ST angiotensin antagonist benzmidazole deriv **cerebrovascular** failure; capsule candesartan cilexetil **cerebrovascular** failure prevention
IT Drug delivery systems
(capsules; preventives for recurrence of **cerebrovascular** failure contg. benzimidazoles as **angiotensin II** antagonists)
IT Brain, disease
(**cerebrovascular**; preventives for recurrence of **cerebrovascular** failure contg. benzimidazoles as **angiotensin II** antagonists)
IT Drug delivery systems
(tablets; preventives for recurrence of **cerebrovascular** failure contg. benzimidazoles as **angiotensin II** antagonists)
IT 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)

L1 ANSWER 31 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:864914 Document No. 135:44517 Relationship between **angiotensin II** type I receptor gene and **cerebral infarction** in Chinese. Zhang, Chen; Wang, Huiyuan; Luo, Bing (Department of Neurology, The Affiliated Hospital of Quingdao University Medical College, Tsingtao, 266003, Peop. Rep. China). Qingdao Daxue Yixueyuan Xuebao, 36(3), 164-166 (Chinese) 2000. CODEN: QDYXAE. Publisher: Qingdao Daxue Yixueyuan Xuebao Bianjibu.
AB Objective: To ascertain the relationship between **angiotensin II** type 1 receptor (AT1R) gene polymorphism and **cerebral infarction** (CI) in Chinese. Methods 196 cases were analyzed by polymerase chain reaction,digestion of restriction enzyme and electrophesis for the 1166C variation at the 3'-untranslated region of AT1R gene. Results: The genotype frequencies of 1166A/1166A, 1166A/1166C, 1166C/1166C were 0.759 5 (60/79), 0.215 2 (17/79), 0.025 3 (2/79) in the control; 0.532 3 (33/62), 0.306 5(19/62), 0.161 3 (10/62) in the CI and 0.545 5(30/55), 0.400 0 (22/55), 0.054 5 (3/55)in the HTN group resp. The allelic gene frequency of 1166C was 0.132 9 in the control group, 0.314 5 in the CI group and 0.254 5 in the HTN. There was significant increase in 1166C genotype frequency between CI and control (.CHI.2 = 11.3992, P < 0.01), HTN and control (.CHI.2 = 6.759 3, P < 0.05); and allelic frequency of 1166C between CI and control (.CHI.2 = 13.679 7, P < 0.01), HTN and control (.CHI.2 = 6.421 8, P < 0.05). In female,the allelic gene frequency of 1166C was 0.102 6 in the control, 0.333 3 in the CI and 0.333 3 in the HTN group. There was significant increase in allelic frequency of 1166C between female CI and control (.CHI.2 = 11.543 3, P < 0.01), HTN and control (.CHI.2 = 11.166 8, P < 0.01). Conclusion: AT1R polymorphism contributes to the development of CI, esp. in the female.
TI Relationship between **angiotensin II** type I receptor gene and **cerebral infarction** in Chinese
AB Objective: To ascertain the relationship between **angiotensin II** type 1 receptor (AT1R) gene polymorphism and **cerebral infarction** (CI) in Chinese. Methods 196 cases were analyzed by polymerase chain reaction,digestion of restriction enzyme and electrophesis for the 1166C. . .
ST **angiotensin II** receptor gene polymorphism brain infarction
IT Angiotensin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AT1; relationship between **angiotensin II** type I receptor gene and **cerebral infarction** in Chinese humans)
IT Gene, animal
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(AT1R; relationship between **angiotensin II** type I receptor gene and **cerebral infarction** in Chinese humans)
IT Brain, disease
(infarction; relationship between **angiotensin II** type I receptor gene and **cerebral infarction** in Chinese humans)

L1 ANSWER 31 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT Genetic polymorphism
Genotypes
(relationship between **angiotensin II** type I receptor gene and **cerebral infarction** in Chinese humans)
IT 11128-99-7, **angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(relationship between **angiotensin II** type I receptor gene and **cerebral infarction** in Chinese humans)

L1 ANSWER 32 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
AB . . . failure. Currently, 2 classes of drugs work by blocking the RAAS, albeit by differing mechanisms: angiotensin-converting enzyme (ACE) inhibitors and **angiotensin II** angiotensin type 1 receptor blockers (ARBs). The goal of this study was to assess the comparative efficacy and tolerability of. . . >110 mm Hg or sitting systolic blood pressure (SBP) >200 mm Hg, angina pectoris, myocardial infarction, cardiac procedure, stroke, or **transient ischemic attack** within 6 mo of randomization, as well as other preexisting or present severe medical or psychol. conditions. Patients were randomly. . .

L1 ANSWER 32 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:858350 Document No. 135:40690 A multicenter, randomized, double-blind study of the antihypertensive efficacy and tolerability of irbesartan in patients aged .gtoreq.65 years with mild to moderate hypertension.
Lacourciere, Yves (Hypertension Unit, Centre Hospitalier Universitaire Laval, Quebec City, QC, Can.). Clinical Therapeutics, 22(10), 1213-1224 (English) 2000. CODEN: CLTHDG. ISSN: 0149-2918. Publisher: Excerpta Medica, Inc..
AB Blockade of the renin-angiotensin-aldosterone system (RAAS) is the preferred mechanism of action for controlling hypertension in select groups of patients, including those with diabetic nephropathy and heart failure. Currently, 2 classes of drugs work by blocking the RAAS, albeit by differing mechanisms: angiotensin-converting enzyme (ACE) inhibitors and **angiotensin II** angiotensin type 1 receptor blockers (ARBs). The goal of this study was to assess the comparative efficacy and tolerability of the ARB irbesartan and the ACE inhibitor enalapril in patients .gtoreq.65 yr of age with mild to moderate hypertension (sitting diastolic blood pressure [DBP], 95 to 110 mm Hg). Elderly (.gtoreq.65 yr of age) patients were recruited from 26 Canadian study centers for a randomized, double-blind, 8-wk clin. trial. Exclusion criteria included sitting DBP >110 mm Hg or sitting systolic blood pressure (SBP) >200 mm Hg, angina pectoris, myocardial infarction, cardiac procedure, stroke, or **transient ischemic attack** within 6 mo of randomization, as well as other preexisting or present severe medical or psychol. conditions. Patients were randomly assigned to receive a single daily dose of irbesartan 150 mg (n = 70) or enalapril 10 mg (n = 71) with treatment doses of study drugs doubled at week 4 for sitting DBP .gtoreq.90 mm Hg. Redns. from baseline blood pressure measurements at trough (24.+-.3 h after the last dose of medication) were assessed for sitting DBP and sitting SBP. Comparative tolerability to study drugs was also assessed. The intent-to-treat anal. demonstrated similar redns. at week 8 in both DBP and SBP for both groups. For the primary efficacy anal. of sitting DBP, there was a mean redn. from baseline of 9.6 mm Hg and 9.8 mm Hg for the irbesartan and enalapril groups, resp. (P = 0.93). The mean redn. from baseline in sitting SBP was 10.1 mm Hg and 11.6 mm Hg for the irbesartan and enalapril groups, resp. (P = 0.54). Normalization rates (sitting DBP <90 mm Hg) at week 8 did not differ between groups (52.9% in the irbesartan group and 54.9% in the enalapril group; P = 0.81). No statistical difference existed between the 2 groups with respect to serious adverse events or discontinuations due to adverse events. Irbesartan was assocd. with a significantly lower incidence of cough than was enalapril (4.3% vs. 15.5%, resp.; P = 0.046). Irbesartan is an effective and well-tolerated antihypertensive for elderly patients with mild to moderate hypertension. This study establishes that irbesartan has better tolerability than enalapril with respect to cough and suggests that irbesartan is as effective at lowering blood pressure but better tolerated than an ACE inhibitor in hypertensive patients .gtoreq.65 yr of age.

L1 ANSWER 33 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:746952 Document No. 134:51217 **Angiotensin II** AT1 blockade normalizes **cerebrovascular** autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats.
Nishimura, Yasuaki; Ito, Takeshi; Saavedra, Juan M. (Section on Pharmacology, National Institute of Mental Health, Bethesda, MD, 20892, USA). Stroke, 31(10), 2478-2486 (English) 2000. CODEN: SJCCA7. ISSN: 0039-2499. Publisher: Lippincott Williams & Wilkins.
AB Background and Purpose- **Angiotensin II**, through stimulation of AT1 receptors, not only controls blood pressure but also modulates **cerebrovascular** flow. We sought to det. whether selective AT1 antagonists could be therapeutically advantageous in brain ischemia during chronic hypertension. Methods- We pretreated spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto controls with the AT1 antagonist candesartan (CV-11974), 0.5 mg/kg per day, for 3 to 14 days, via s.c. implanted osmotic minipumps. We analyzed cerebral blood flow by laser-Doppler flowmetry, cerebral stroke in SHR after occlusion of the middle cerebral artery with reperfusion, and brain AT1 receptors by quant. autoradiog. Results- Candesartan treatment normalized blood pressure and the shift toward higher blood pressures at both the upper and lower limits of **cerebrovascular** autoregulation in SHR. Candesartan pretreatment of SHR for 14 days partially prevented the decrease in blood flow in the marginal zone of ischemia and significantly reduced the vol. of total and cortical infarcts after either 1 or 2 h of middle cerebral artery occlusion with reperfusion, relative to untreated SHR, resp. This treatment also significantly reduced brain edema after 2 h of middle cerebral artery occlusion with reperfusion. In SHR, candesartan markedly decreased AT1 binding in areas inside (nucleus of the solitary tract) and outside (area postrema) the blood-brain barrier and in the middle cerebral artery. Conclusions- Pretreatment with an AT1 antagonist protected hypertensive rats from brain ischemia by normalizing the cerebral blood flow response, probably through AT1 receptor blockade in cerebral vessels and in brain areas controlling **cerebrovascular** flow during stroke.
TI **Angiotensin II** AT1 blockade normalizes **cerebrovascular** autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats
AB Background and Purpose- **Angiotensin II**, through stimulation of AT1 receptors, not only controls blood pressure but also modulates **cerebrovascular** flow. We sought to det. whether selective AT1 antagonists could be therapeutically advantageous in brain ischemia during chronic hypertension. Methods- . . . Candesartan treatment normalized blood pressure and the shift toward higher blood pressures at both the upper and lower limits of **cerebrovascular** autoregulation in SHR. Candesartan pretreatment of SHR for 14 days partially prevented the decrease in blood flow in the marginal. . . by normalizing the cerebral blood flow response, probably through AT1 receptor blockade in cerebral vessels and in brain areas controlling **cerebrovascular** flow during stroke.
IT Angiotensin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

L1 ANSWER 33 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
(AT1; **angiotensin II** AT1 blockade normalizes **cerebrovascular** autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats)
IT Anti-ischemic agents
Hypertension
(**angiotensin II** AT1 blockade normalizes **cerebrovascular** autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats)
IT Circulation
(cerebral; **angiotensin II** AT1 blockade normalizes **cerebrovascular** autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats)
IT Brain, disease
(ischemia; **angiotensin II** AT1 blockade normalizes **cerebrovascular** autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats)
IT Artery
(middle cerebral; candesartan effect on cerebral **angiotensin II** AT1 receptors and **cerebrovascular** autoregulation in spontaneously hypertensive rats)
IT Brain
(nucleus tractus solitarii; candesartan effect on cerebral **angiotensin II** AT1 receptors and **cerebrovascular** autoregulation in spontaneously hypertensive rats)
IT Brain
(postrema area; candesartan effect on cerebral **angiotensin II** AT1 receptors and **cerebrovascular** autoregulation in spontaneously hypertensive rats)
IT 11128-99-7, **Angiotensin II**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**angiotensin II** AT1 blockade normalizes **cerebrovascular** autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats)
IT 139481-59-7, CV-11974
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**angiotensin II** AT1 blockade normalizes **cerebrovascular** autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats)

L1 ANSWER 34 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

L1 ANSWER 34 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:743385 Document No. 134:305109 Reducing cardiovascular morbidity and mortality in the elderly. Trenkwalder, Peter (Department of Medicine, Starnberg Hospital, University of Munich, Starnberg, Germany). Blood Pressure, Supplement (1), 40-43 (English) 2000. CODEN: BPSUEY. ISSN: 0803-8023. Publisher: Scandinavian University Press.
AB Candesartan cilexetil is highly effective at lowering blood pressure, while maintaining placebo-like tolerability, in a wide range of patient groups. Although the benefit of lowering blood pressure in elderly patients with moderate hypertension has been demonstrated in several large-scale clin. trials, elderly patients with mild hypertension have rarely been studied. The high incidence of cardiovascular and **cerebrovascular** mortality and morbidity, including dementia, in the elderly means that control of blood pressure is particularly important in this patient group. A major new international clin. trial - SCOPE (Study on Cognition and Prognosis in the Elderly) - has therefore been initiated. This is a prospective, randomized, double-blind, parallel comparison of the effects of candesartan cilexetil, 8 or 16 mg once daily, and placebo in about 5000 patients who will be followed for a mean of 2.5 yr. SCOPE is the first study designed to assess the effect of antihypertensive therapy in elderly patients (70-89 yr of age) with mild hypertension (sitting systolic blood pressure of 160-179 mmHg and/or sitting diastolic blood pressure of 90-99 mmHg). The primary objective of the study is to det. the effect of candesartan cilexetil on major cardiovascular events (cardiovascular death, non-fatal stroke and myocardial infarction, and silent myocardial infarction), while an important secondary objective is to det. the effect of such treatment on the prevention of cognitive impairment. SCOPE should provide definitive evidence of the cardiovascular and **cerebrovascular** benefits of treating mildly hypertensive elderly patients with **angiotensin II** type I receptor blockers, which not only reduce blood pressure, but may also provide significant protection from the neg. effects of **angiotensin II** on target organs.
AB . . . in several large-scale clin. trials, elderly patients with mild hypertension have rarely been studied. The high incidence of cardiovascular and **cerebrovascular** mortality and morbidity, including dementia, in the elderly means that control of blood pressure is particularly important in this patient. . . . the effect of such treatment on the prevention of cognitive impairment. SCOPE should provide definitive evidence of the cardiovascular and **cerebrovascular** benefits of treating mildly hypertensive elderly patients with **angiotensin II** type I receptor blockers, which not only reduce blood pressure, but may also provide significant protection from the neg. effects of **angiotensin II** on target organs.
IT Angiotensin receptor antagonists
(**angiotensin II**; effect of candesartan cilexetil on major cardiovascular events and on the prevention of cognitive impairment in the elderly)

L1 ANSWER 35 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:692024 Document No. 134:172549 **Angiotensin II** and renin-angiotensin system antagonist affect the cerebral circulation. Adzhienko, L. M. (Inst. Pharacol., RAMS, Moscow, 125315, Russia). Eksperimental'naya i Klinicheskaya Farmakologiya, 63(4), 74-79 (Russian) 2000. CODEN: EKFAE9. ISSN: 0869-2092. Publisher: Izdatel'stvo Folium.
AB A review with 56 refs outlining the significant role that the renin-angiotensin system (RAS) plays in the regulation of cerebral circulation. The pharmacol. correction of **cerebrovascular** disorders by using RAS antagonists is discussed.
TI **Angiotensin II** and renin-angiotensin system antagonist affect the cerebral circulation
AB . . . outlining the significant role that the renin-angiotensin system (RAS) plays in the regulation of cerebral circulation. The pharmacol. correction of **cerebrovascular** disorders by using RAS antagonists is discussed.
IT Blood vessel
Renin-angiotensin system
(**angiotensin II** and renin-angiotensin system antagonist affect the cerebral circulation)
IT Circulation
(cerebral; **angiotensin II** and renin-angiotensin system antagonist affect the cerebral circulation)
IT 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**angiotensin II** and renin-angiotensin system antagonist affect the cerebral circulation)

L1 ANSWER 36 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:670765 Document No. 134:172536 Rationale for **angiotensin II** receptor blockers in patients with low-renin hypertension. Jamerson, Kenneth A. (University of Michigan Medical Center, Ann Arbor, MI, 48109-0357, USA). American Journal of Kidney Diseases, 36(3, Suppl. 1), S24-S30 (English) 2000. CODEN: AJKDDP. ISSN: 0272-6386. Publisher: W. B. Saunders Co..
AB A review with 32 refs. African Americans outrank other ethnic groups in the United States in prevalence, early onset, and severity of hypertension. Furthermore, African Americans suffer the highest rates of mortality from cardiovascular, **cerebrovascular**, and end-stage renal disease. The recently concluded Heart Outcomes Prevention Evaluation (HOPE) study reports that the angiotensin-converting enzyme (ACE) inhibitor ramipril significantly reduced morbidity and mortality in a broad range of patients at high risk for cardiovascular events. These results strengthen the case for increasing the use of ACE inhibitor therapy. In accord with the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) guidelines, antihypertensive monotherapy for African Americans is based on the known ability of diuretics and calcium channel blockers to produce greater redns. in blood pressure in this population than those attainable with beta blockers and ACE inhibitors. The national guidelines also suggest ACE inhibitors for all hypertensive patients with left ventricular dysfunction or nephropathy, which implies that African Americans must cross a clin. threshold to become candidates for these agents. The rationale for delaying ACE inhibitor therapy is due in part to a perceived unique pathobiol. in hypertensive African Americans: an excess prevalence of salt sensitivity, hypervolemia, and low plasma renin activity (PRA). At first glance, it would seem intuitive to avoid agents that further depress the renin-angiotensin system (RAS) and choose agents that reduce plasma vol. However, most hypertensive African Americans are not hypovolemic. Furthermore, dietary sodium restriction and diuretic therapy raise PRA and improve the response to ACE inhibitors. The overall aim of this article is to explain the rationale for expanded use of drugs that block the RAS in African Americans and low-renin populations.
TI Rationale for **angiotensin II** receptor blockers in patients with low-renin hypertension
AB . . . States in prevalence, early onset, and severity of hypertension. Furthermore, African Americans suffer the highest rates of mortality from cardiovascular, **cerebrovascular**, and end-stage renal disease. The recently concluded Heart Outcomes Prevention Evaluation (HOPE) study reports that the angiotensin-converting enzyme (ACE) inhibitor. . .
ST review **angiotensin II** receptor blocker low renin hypertension
IT Angiotensin receptor antagonists
(**angiotensin II**; rationale for **angiotensin II** receptor blockers in patients with low-renin hypertension)
IT Antihypertensives

L1 ANSWER 36 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
Hypertension
(rationale for **angiotensin II** receptor blockers in patients with low-renin hypertension)
IT 9015-94-5, Renin, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(rationale for **angiotensin II** receptor blockers in patients with low-renin hypertension)

L1 ANSWER 37 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:506952 Document No. 134:28160 The relationship between **angiotensin II** type 1 receptor gene polymorphism and Chinese essential hypertension. Zhong, Ya; Ha, Daiwen (Department of Gerontology,Second Affiliated Hospital, Hubei Medical University, 430071, Peop. Rep. China). Hubei Yike Daxue Xuebao, 21(2), 124-127 (Chinese) 2000. CODEN: HYDXFU. ISSN: 1008-0724. Publisher: Hubei Yike Daxue Xuebao Bianjibu.
AB Objective: To identify the polymorphism of **angiotensin II** types 1 receptor (AT1R) gene in Chinese essential hyper-tension. Methods: This study included 70 hypertensive (involved 34 hypertensives complicated with coronary artery disease) and 70 normotensive subjects. AT1R genotype was analyzed by polymerase chain reaction, digestion of restriction enzyme and electrophoresis. Results: The frequencies of C allele among the essential hyper-tension group (12.9%) were higher than those among the control group (3.6%, P<0.005). The frequencies of C allele were no difference between hypertensives complicated with coronary artery disease and hypertensives without cardiovascular or **cerebrovascular** diseases. Conclusion: The AT1R gene A1166/C polymorphism is probably an important hereditary factor in Chinese essential hypertension.
TI The relationship between **angiotensin II** type 1 receptor gene polymorphism and Chinese essential hypertension
AB Objective: To identify the polymorphism of **angiotensin II** types 1 receptor (AT1R) gene in Chinese essential hyper-tension. Methods: This study included 70 hypertensive (involved 34 hypertensives complicated with. . . The frequencies of C allele were no difference between hypertensives complicated with coronary artery disease and hypertensives without cardiovascular or **cerebrovascular** diseases. Conclusion: The AT1R gene A1166/C polymorphism is probably an important hereditary factor in Chinese essential hypertension.
ST **angiotensin II** receptor gene polymorphism essential hypertension
IT Gene, animal
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(AT1R (**angiotensin II** type 1 receptor); relationship between **angiotensin II** type 1 receptor gene polymorphism and Chinese human essential hypertension)
IT Genetic polymorphism
(AT1R gene A1166/C polymorphism; relationship between **angiotensin II** type 1 receptor gene polymorphism and Chinese human essential hypertension)
IT Angiotensin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AT1; relationship between **angiotensin II** type 1 receptor gene polymorphism and Chinese human essential hypertension)
IT Hypertension
(essential; relationship between **angiotensin II** type 1 receptor gene polymorphism and Chinese human essential hypertension)

L1 ANSWER 37 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT Genotypes
(relationship between **angiotensin II** type 1 receptor gene polymorphism and Chinese human essential hypertension)

L1 ANSWER 38 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:390959 Document No. 133:12837 Clinical pharmacokinetics of **angiotensin II** (AT1) receptor blockers in hypertension. Israili, Z. H. (Emory University School of Medicine, Atlanta, GA, 30303, USA). Journal of Human Hypertension, 14(Suppl. 1), S73-S86 (English) 2000. CODEN: JHHYEN. ISSN: 0950-9240. Publisher: Nature Publishing Group.

AB A review with 174 refs. **Angiotensin II** receptor blockers (ARBs) represent a new class of effective and well tolerated orally active antihypertensive agents. Recent clin. trials have shown the added benefits of ARBs in hypertensive patients (redn. in left ventricular hypertrophy, improvement in diastolic function, decrease in ventricular arrhythmias, redn. in microalbuminuria, and improvement in renal function), and cardioprotective effect in patients with heart failure. Several large long-term studies are in progress to assess the beneficial effects of ARBs on cardiac hypertrophy, renal function, and cardiovascular and **cerebrovascular** morbidity and mortality in hypertensive patients with or without diabetes mellitus, and the value of these drugs in patients with heart disease and diabetic nephropathy. The ARBs specifically block the interaction of **angiotensin II** at the AT, receptor, thereby relaxing smooth muscle, increasing salt and water excretion, reducing plasma vol., and decreasing cellular hypertrophy. These agents exert their blood pressure-lowering effect mainly by reducing peripheral vascular resistance usually without a rise in heart rate. Most of the com. available ARBs control blood pressure for 24 h after once daily dosing. Sustained efficacy of blood pressure control, without any evidence of tachyphylaxis, has been demonstrated after long-term administration (3 yr) of some of the ARBs. The efficacy of ARBs is similar to that of thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors or calcium channel blockers in patients with similar degree of hypertension. Higher daily doses, dietary salt restriction, and concomitant diuretic or ACE inhibitor administration amplify the antihypertensive effect of ARBs. The ARBs have a low incidence of adverse effects (headache, upper respiratory infection, back pain, muscle cramps, fatigue and dizziness), even in the elderly patients. After the approval of losartan, five other ARBs (candesartan cilexetil, eprosartan, irbesartan, telmisartan, and valsartan) and three combinations with hydrochlorothiazide (irbesartan, losartan and valsartan) have been approved as antihypertensive agents, and some 28 compds. are in various stages of development. The ARBs are non-peptide compds. with varied structures; some (candesartan, losartan, irbesartan, and valsartan) have a common tetrazolo-biphenyl structure. Except for irbesartan, all active ARBs have a carboxylic acid group. Candesartan cilexetil is a prodrug, while losartan has a metabolite (EXP3174) which is more active than the parent drug. No other metabolites of ARBs contribute significantly to the antihypertensive effect. The variation in the mol. structure of the ARBs results in differences in the binding affinity to the receptor and pharmacokinetic profiles. The differences obsd. in lipid soly., absorption/distribution, plasma protein binding, bioavailability, biotransformation, plasma half-life, and systemic elimination influence the time of onset, duration of action, and efficacy of the ARBs. On the basis of the daily mg dose, the anti-hypertensive potency of the ARBs follows the sequence: candesartan cilexetil > telmisartan losartan > irbesartan valsartan > eprosartan. After oral administration, the ARBs are rapidly absorbed (time for peak plasma levels = 0.5-4 h) but they have a wide range of bioavailability (from a low of 13% for eprosartan to a high of 60-80% for irbesartan); food does not influence the bioavailability, except for valsartan (a redn. of 40-50%) and eprosartan (increase). A limited dose-peak plasma levels/areas under the plasma level-time curve proportionality is obsd. for some of the ARBs. Most of these drugs have high plasma protein binding (95-100%); irbesartan has the lowest binding among the group (90%). The steady-state vols. of distribution vary from a low of 9 L (candesartan) to a high of 500 L (telmisartan). Plasma elimination half-life is short for candesartan cilexetil and losartan (1-4 h), intermediate for eprosartan and valsartan (5-10 h), and longer for candesartan, irbesartan and telmisartan (11-38 h); the active metabolite of losartan has a longer half-life than for the parent drug. The drugs and their active metabolites do not accumulate to a significant extent after repeated dosing, except for telmisartan (100%).

Most of the orally administered dose of ARBs is excreted via bile into the feces; from 2% (telmisartan) to 33% (candesartan) of the oral dose is excreted in the urine. In most cases, changes in pharmacokinetic parameters due to aging, mild to moderate renal disease and heart failure do not require dosage modification; dosage has to be individualized for eprosartan, losartan, telmisartan and valsartan in patients with hepatic disease. In general, pharmacokinetic drug-drug interactions are rare, with the exception of combination of digoxin and telmisartan. The ARBs are an important treatment option for hypertension, being relatively safe and efficacious. The beneficial effects of the ARB therapy go beyond blood pressure control. They may prove to have beneficial hemodynamic and neurohormonal effects in heart failure and provide renoprotection in diabetic nephropathy.

L1 ANSWER 38 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

TI Clinical pharmacokinetics of **angiotensin II** (AT1) receptor blockers in hypertension

AB A review with 174 refs. **Angiotensin II** receptor blockers (ARBs) represent a new class of effective and well tolerated orally active antihypertensive agents. Recent clin. trials have. . . long-term studies are in progress to assess the beneficial effects of ARBs on cardiac hypertrophy, renal function, and cardiovascular and **cerebrovascular** morbidity and mortality in hypertensive patients with or without diabetes mellitus, and the value of these drugs in patients with heart disease and diabetic nephropathy. The ARBs specifically block the interaction of **angiotensin II** at the AT, receptor, thereby relaxing smooth muscle, increasing salt and water excretion, reducing plasma vol., and decreasing cellular hypertrophy. . .

IT Angiotensin receptor antagonists
(**angiotensin II**; clin. pharmacokinetics of **angiotensin II** (AT1) receptor blockers in hypertension)

IT Antihypertensives
(clin. pharmacokinetics of **angiotensin II** (AT1) receptor blockers in hypertension)

L1 ANSWER 39 OF 123 CAPLUS COPYRIGHT 2003 ACS

2000:281826 Document No. 133:236176 Response of the rabbit arteriosclerotic basilar artery to vasoactive substances. Ozaki, Masashige (Dep. Neurosurgery, Osaka Medical College, Japan). Osaka Ika Daigaku Zasshi, 58(3), 25-35 (Japanese) 1999. CODEN: OIDZAU. ISSN: 0030-6118. Publisher: Osaka Ika Daigaku Igakkai.

AB The present study was performed to examine the influence of arteriosclerosis on vascular tone and to investigate the possible involvement of arteriosclerosis in cerebral vasospasm in a new line of Watanabe heritable hyperlipidemic (WHHL) rabbits. For these purposes, vascular responses of isolated basilar artery rings to vasoconstricting and vasodilating substances were compared in WHHL and age-matched Japanese white (JW) rabbits. In WHHL rabbit basilar arteries, endothelium-dependent relaxations caused by acetylcholine were less potent than those seen in the JW rabbit arteries, while those caused by substance P did not differ between the two strains. Endothelium-independent relaxations caused by sodium nitroprusside, an NO donor, and beraprost, a prostacyclin analog, did not differ. Contractions induced by endothelin (ET)-1 and by histamine were potent in the WHHL than in the JW rabbit arteries. However, contractions caused by serotonin, neuropeptide Y, and **angiotensin II** were not different. Histol. observations by light microscopy revealed that arteriosclerotic lesions contg. fibromatous plaque were obsd. in WHHL, but not JW, basilar arteries. It is suggested that endothelial functions responsible for NO synthesis and release do not seem to be impaired in arteriosclerotic cerebral arteries, but potentiated responses to ET-1 and histamine may promote cerebral vasospasm after **subarachnoid hemorrhage**.

AB . . . histamine were potent in the WHHL than in the JW rabbit arteries. However, contractions caused by serotonin, neuropeptide Y, and **angiotensin II** were not different. Histol. observations by light microscopy revealed that arteriosclerotic lesions contg. fibromatous plaque were obsd. in WHHL, but. . . seem to be impaired in arteriosclerotic cerebral arteries, but potentiated responses to ET-1 and histamine may promote cerebral vasospasm after **subarachnoid hemorrhage**.

IT Brain, disease
(cerebrum, vasospasm; basilar artery response to vasoactive substances in hyperlipidemic rabbits in relation to arteriosclerosis involvement in cerebral vasospasm after **subarachnoid hemorrhage**)

L1 ANSWER 40 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:209908 Document No. 132:241973 Pharmaceutical compositions containing an **angiotensin II** AT1 receptor antagonist and an antiplatelet agent. Cazaubon, Catherine; Herbert, Jean-Marc; Nisato, Dino (Sanofi-Synthelabo, Fr.). PCT Int. Appl. WO 2000016773 A1 20000330. 25 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (French). CODEN: PIXXD2. APPLICATION: WO 1999-FR2128 19990908. PRIORITY: FR 1998-11747 19980921.

AB Pharmaceutical compns. contg. an **angiotensin II** AT1 receptor antagonist and an antiplatelet agent are claimed. The antithrombotic efficacy of 100 mg/kg irbesartan and 10 mg/kg clopidogrel hydrogen sulfate is shown. A tablet contained irbesartan 50, clopidogrel hydrogen sulfate 97.5, lactose 48.5, maize starch 44, talc 25, polyvinylpyrrolidone 9, anhyd. colloidal silica 0.5, and magnesium stearate 3 mg.

TI Pharmaceutical compositions containing an **angiotensin II** AT1 receptor antagonist and an antiplatelet agent

AB Pharmaceutical compns. contg. an **angiotensin II** AT1 receptor antagonist and an antiplatelet agent are claimed. The antithrombotic efficacy of 100 mg/kg irbesartan and 10 mg/kg clopidogrel. . .

IT Angiotensin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AT1, antagonists; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Heart, disease
(angina pectoris; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Artery
(angioplasty; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Antiarteriosclerotics
(antiatherosclerotics; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Drug delivery systems
(capsules; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Brain, disease
(**cerebrovascular**; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

L1 ANSWER 40 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
(synergic; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Antihypertensives
(synergistic; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Drug delivery systems
(tablets; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Embolism
(thromboembolism; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Heart, disease
(ventricular fibrillation; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Integrins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.IIb.beta.3, antagonists; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT 53885-35-1, Ticlopidine hydrochloride 120202-66-6, Clopidogrel hydrogen sulfate 138402-11-6, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

L1 ANSWER 40 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT Mental disorder
(dementia; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Eye, disease
(diabetic retinopathy; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Cardiovascular system
(disease; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Prosthetic materials and Prosthetics
(endovascular; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Heart, disease
(failure; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Dialysis
(hemodialysis; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Heart, disease
(infarction; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Drug delivery systems
(injections, i.v.; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Vein
(insufficiency; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Drug delivery systems
(oral; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Drug delivery systems
(parenterals; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Artery, disease
(peripheral; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Antidiabetic agents
Brain, disease
Glaucoma (disease)
Platelet aggregation inhibitors
(pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Artery, disease
(restenosis; pharmaceutical compns. contg. **angiotensin II** AT1 receptor antagonist and antiplatelet agent)

IT Anticoagulants

L1 ANSWER 41 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:140122 Document No. 133:72264 Renin-angiotensin-aldosterone system gene polymorphisms and hypertension in Hong Kong Chinese. Thomas, G. Neil; Young, Robert P.; Tomlinson, Brian; Woo, Kam Sang; Sanderson, John E.; Critchley, Julian A. J. H. (Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, Peop. Rep. China). Clinical and Experimental Hypertension, 22(1), 87-97 (English) 2000. CODEN: CEHYER. ISSN: 1064-1963. Publisher: Marcel Dekker, Inc..

AB In Chinese populations, hypertension is common and is a major risk factor for **cerebrovascular** and coronary heart disease. The renin-angiotensin-aldosterone system (RAAS) helps maintain blood pressure and salt homeostasis and appears important in the pathogenesis of hypertension and some forms of vascular disease. We investigated three RAAS gene polymorphisms, the angiotensin-converting enzyme (ACE) insertion/deletion, angiotensinogen (AGT) M235T and **angiotensin II** type 1 receptor A1166C polymorphisms in 232 hypertensive and 178 normotensive Chinese subjects. The hypertensives were generally more obese and dyslipidemic. No significant differences in genotype or allele frequencies for any of the polymorphisms were identified between the groups, nor was there any interactive contribution to blood pressure by the ACE and AGT polymorphisms. However, there were large differences in genotype and allele frequencies between the healthy Chinese and published data for equiv. Caucasian populations. These findings suggest these polymorphisms are unlikely to be involved in the pathogenesis of hypertension in Chinese.

AB In Chinese populations, hypertension is common and is a major risk factor for **cerebrovascular** and coronary heart disease. The renin-angiotensin-aldosterone system (RAAS) helps maintain blood pressure and salt homeostasis and appears important in the. . . some forms of vascular disease. We investigated three RAAS gene polymorphisms, the angiotensin-converting enzyme (ACE) insertion/deletion, angiotensinogen (AGT) M235T and **angiotensin II** type 1 receptor A1166C polymorphisms in 232 hypertensive and 178 normotensive Chinese subjects. The hypertensives were generally more obese and. . .

IT Aging, animal
Allele frequency
Genetic polymorphism
Genotypes
Obesity
Population genetics
(ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)

IT Gene, animal
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(AGT; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)

IT Angiotensin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AT1; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong

L1 ANSWER 41 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
Chinese)
IT Gene, animal
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(AT1R; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)
IT Gene, animal
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(Ace; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)
IT Glycerides, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(blood; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)
IT Lipids, biological studies
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(dyslipidemia; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)
IT Lipoproteins
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(high-d.; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)
IT 57-88-5, Cholesterol, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)
IT 9015-82-1, Angiotensin-converting enzyme 11002-13-4, Angiotensinogen (protein renin substrate)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)
IT 50-99-7, D-Glucose, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(blood; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong

L1 ANSWER 41 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
Chinese)
IT 69-93-2, Uric acid, biological studies 7440-23-5, Sodium, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(plasma; ACE, angiotensinogen and **angiotensin II** type 1 receptor gene polymorphisms in hypertension in human Hong Kong Chinese)

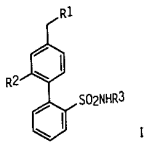
L1 ANSWER 42 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:111307 Document No. 132:146719 Role of renin-angiotensin system in regulation of cerebral circulation. Takishita, Shuichi (Div. Hypertension Nephrol., Natl. Cardiovasc. Cent., Japan). Horumon to Rinsho, 48(2), 125-132 (Japanese) 2000. CODEN: HORIAE. ISSN: 0045-7167. Publisher: Igaku no Sekaisha.
AB A review with 28 refs., on regulatory mechanism of cerebral circulation, and pathophysiol. roles of renin-angiotensin system therein. The **cerebrovascular** and cerebral circulation-protecting effects of ACE inhibitors and AT1 antagonists are also discussed.
AB A review with 28 refs., on regulatory mechanism of cerebral circulation, and pathophysiol. roles of renin-angiotensin system therein. The **cerebrovascular** and cerebral circulation-protecting effects of ACE inhibitors and AT1 antagonists are also discussed.
IT Angiotensin receptor antagonists
(**angiotensin II**; pathophysiol. role of renin-angiotensin system in regulation of cerebral circulation)

L1 ANSWER 43 OF 123 CAPLUS COPYRIGHT 2003 ACS
2000:64537 Document No. 132:342571 Therapeutic options in minimizing left ventricular hypertrophy. Devereux, Richard B. (Division of Cardiology, New York Presbyterian Hospital/Cornell Medical Center, New York, NY, 10021, USA). American Heart Journal, 139(1, Pt. 2), S9-S14 (English) 2000. CODEN: AHJOA2. ISSN: 0002-8703. Publisher: Mosby, Inc..
AB A review with 29 refs. Left ventricular hypertrophy (LVH), a target-organ response to chronic pressure or vol. overload, is assocd. with its own independent risks of death in patients with hypertension. Numerous studies have shown that LVH increases the risk of coronary heart disease, congestive heart failure, stroke or **transient ischemic attack**, all-cause deaths, and sudden death. Although the mechanisms by which LVH develops are incompletely understood, the renin-angiotensin system may play on important role. All major classes of antihypertensive agents (calcium channel blockers, diuretics, .beta.-blockers, angiotensin-converting enzyme inhibitors) can cause LVH regression but not all to the same degree. Angiotensin-converting enzyme inhibitors may provide the most pronounced redn. in left ventricular mass per mm of mercury of blood pressure redn. In addn., animal studies and human trials show promise for the regression of LVH with the use of angiotensin receptor blockers (ARBs). Becuase ARBs act specifically on the AT1 receptor, **angiotensin II** can exert its favorable effects on cell growth inhibition through the AT2 receptor. One small study that compared the ARB valsartan with atenolol found significant regression of LVH with the ARB by 8 mo of treatment.
AB . . . with hypertension. Numerous studies have shown that LVH increases the risk of coronary heart disease, congestive heart failure, stroke or **transient ischemic attack**, all-cause deaths, and sudden death. Although the mechanisms by which LVH develops are incompletely understood, the renin-angiotensin system may play. . . the regression of LVH with the use of angiotensin receptor blockers (ARBs). Becuase ARBs act specifically on the AT1 receptor, **angiotensin II** can exert its favorable effects on cell growth inhibition through the AT2 receptor. One small study that compared the ARB. . .

L1 ANSWER 44 OF 123 CAPLUS COPYRIGHT 2003 ACS

2000:34745 Document No. 132:93309 Preparation of N-isoxazolyl biphenylsulfonamides and related compounds as dual **angiotensin II** and endothelin receptor antagonists.. Murugesan, Natesan; Tellew, John E.; Macor, John E.; Gu, Zhengxiang (Bristol-Myers Squibb Co., USA). PCT Int. Appl. WO 2000001389 A1 20000113, 283 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US15063 19990701. PRIORITY: US 1998-91847 19980706.

GI



I

AB Title compds. (I; R1 = specified oxoimidazolyl, pyridoimidazolyl, pyridylamino, triazolyl, quinolinyloxy, etc.; R2 = H, halo, CHO, alkyl, haloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxy, cyano, OH, NO2, etc.; R3 = heteroaryl; with provisos), were prepd. as dual **angiotensin II** and endothelin receptor antagonists (no data). Thus, 4-BrC6H4CH2OH was coupled with [2-[[(4,5-dimethyl-3-isoxazolyl)[(2-methoxyethoxy)methyl]amino]sulfonyl]phenyl]boronic acid to give N-(4,5-dimethyl-3-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide. This was brominated to give 4'-bromomethyl-N-(4,5-dimethyl-3-isoxazolyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide, which reacted with 2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one hydrochloride followed by deprotection to give 4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide.

TI Preparation of N-isoxazolyl biphenylsulfonamides and related compounds as dual **angiotensin II** and endothelin receptor antagonists.

AB . . . alkyl, haloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxy, cyano, OH, NO2, etc.; R3 = heteroaryl; with provisos), were prepd.

L1 ANSWER 44 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

as dual **angiotensin II** and endothelin receptor antagonists (no data). Thus, 4-BrC6H4CH2OH was coupled with [2-[[(4,5-dimethyl-3-isoxazolyl)[(2-methoxyethoxy)methyl]amino]sulfonyl]phenyl]boronic acid to give N-(4,5-dimethyl-3-isoxazolyl)-4'-(hydroxymethyl)-N-[(2-methoxyethoxy)methyl][1,1'-biphenyl]-2-sulfonamide. This was brominated to. . .

IT Angiotensin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(**angiotensin II**, antagonists; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Endothelin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(antagonists; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Antiarteriosclerotics
(antiatherosclerotics; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Prostate gland
(benign hyperplasia, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Sexual behavior
(disorder, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Heart, disease
(failure, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Kidney, disease
(failure; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Sexual behavior
(impotence, treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Antiasthmatics
Antihypertensives
Antimigraine agents
Antitumor agents
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as

L1 ANSWER 44 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

dual **angiotensin II** and endothelin receptor antagonists)

IT Growth inhibitors, animal
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Meninges
(**subarachnoid hemorrhage**; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT Endotoxemia
Ischemia
(treatment; prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

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|---|---|---|---|---|
| 254737-84-3P | 254737-85-4P | 254737-86-5P | 254737-87-6P | 254737-88-7P |
| 254737-89-8P | 254737-90-1P | 254737-91-2P | 254737-92-3P | 254737-94-5P |
| 254737-96-7P | 254737-98-9P | 254738-00-6P | 254738-03-9P | 254738-05-1P |
| 254738-06-2P | 254738-07-3P | 254738-09-5P | 254738-10-8P | 254738-11-9P |
| 254738-12-0P | 254738-13-1P | 254738-14-2P | 254738-15-3P | 254738-16-4P |
| 254738-17-5P | 254738-18-6P | 254738-19-7P | 254738-20-0P | 254738-21-1P |
| 254738-22-2P | 254738-23-3P | 254738-24-4P | 254738-25-5P | 254738-26-6P |
| 254738-27-7P | 254738-28-8P | 254738-29-9P | 254738-30-2P | 254738-31-3P |
| 254738-32-4P | 254738-33-5P | 254738-34-6P | 254738-35-7P | 254738-36-8P |
| 254738-37-9P | 254738-38-0P | 254738-39-1P | 254738-40-4P | 254738-41-5P |
| 254738-42-6P | 254738-43-7P | 254738-44-8P | 254738-45-9P | 254738-46-0P |
| 254738-47-1P | 254738-48-2P | 254738-49-3P | 254738-50-6P | 254738-51-7P |
| 254738-52-8P | 254738-53-9P | 254738-54-0P | 254738-55-1P | 254738-56-2P |
| 254738-57-3P | 254738-58-4P | 254738-59-5P | 254738-60-8P | 254738-61-9P |
| 254738-62-0P | 254738-63-1P | 254738-64-2P | 254738-65-3P | 254738-66-4P |
| 254738-67-5P | 254738-68-6P | 254738-69-7P | 254738-70-0P | 254738-71-1P |
| 254738-72-2P | 254738-73-3P | 254738-74-4P | 254738-75-5P | 254738-76-6P |
| 254738-78-8P | 254738-79-9P | 254738-80-2P | 254738-81-3P | 254738-82-4P |
| 254738-83-5P | 254738-84-6P | 254738-85-7P | 254738-86-8P | 254738-87-9P |
| 254738-88-0P | 254738-89-1P | 254738-90-4P | 254738-91-5P | 254738-92-6P |
| 254738-93-7P | 254738-94-8P | 254738-95-9P | 254738-96-0P | 254738-97-1P |
| 254738-98-2P | 254738-99-3P | 254739-00-9P | 254739-01-0P | 254739-02-1P |
| 254739-03-2P | 254739-04-3P | 254739-05-4P | 254739-06-5P | 254739-07-6P |
| 254739-08-7P | 254739-09-8P | 254739-10-1P | 254739-11-2P | 254739-12-3P |
| 254739-13-4P | 254739-14-5P | 254739-15-6P | 254739-16-7P | 254739-17-8P |
| 254739-18-9P | 254739-19-0P | 254739-20-3P | 254739-21-4P | 254739-22-5P |
| 254739-23-6P | 254739-24-7P | 254739-25-8P | 254739-26-9P | 254739-27-0P |
| 254739-28-1P | 254739-29-2P | 254739-30-5P | 254739-31-6P | 254739-32-7P |
| 254739-33-8P | 254739-34-9P | 254739-35-0P | 254739-36-1P | 254739-37-2P |
| 254739-38-3P | 254739-39-4P | 254739-40-7P | 254739-41-8P | 254739-42-9P |
| 254739-43-0P | 254739-44-1P | 254739-45-2P | 254739-46-3P | 254739-47-4P |
| 254739-48-5P | 254739-49-6P | 254739-50-9P | 254739-51-0P | 254739-52-1P |
| 254739-53-2P | 254739-54-3P | 254739-55-4P | 254739-56-5P | 254739-57-6P |

L1 ANSWER 44 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

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|---|---|---|---|---|
| 254739-58-7P | 254739-59-8P | 254739-60-1P | 254739-61-2P | 254739-62-3P |
| 254739-63-4P | 254739-64-5P | 254739-65-6P | 254739-66-7P | 254739-67-8P |
| 254739-68-9P | 254739-69-0P | 254739-70-3P | 254739-71-4P | 254739-72-5P |
| 254739-73-6P | 254739-74-7P | 254739-75-8P | 254739-76-9P | 254739-77-0P |
| 254739-79-2P | 254739-80-5P | 254739-81-6P | 254739-82-7P | 254739-83-8P |
| 254739-84-9P | 254739-85-0P | 254739-86-1P | 254739-87-2P | 254739-88-3P |
| 254739-89-4P | 254739-90-7P | 254739-91-8P | 254739-92-9P | 254739-93-0P |
| 254739-94-1P | 254739-95-2P | 254739-96-3P | 254739-97-4P | 254739-98-5P |
| 254739-99-6P | 254740-00-6P | 254740-01-7P | 254740-02-8P | 254740-03-9P |
| 254740-04-0P | 254740-05-1P | 254740-06-2P | 254740-07-3P | 254740-08-4P |
| 254740-09-5P | 254740-10-8P | 254740-11-9P | 254740-12-0P | 254740-15-3P |
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| 254740-29-9P | 254740-30-2P | 254740-31-3P | 254740-32-4P | |

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

| | | | | |
|---|---|---|---|---|
| 254740-33-5P | 254740-34-6P | 254740-35-7P | 254740-36-8P | 254740-37-9P |
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| 254740-43-7P | 254740-44-8P | 254740-45-9P | 254740-46-0P | 254740-47-1P |
| 254740-48-2P | 254740-49-3P | 254740-50-6P | 254740-51-7P | 254740-52-8P |
| 254740-53-9P | 254740-54-0P | 254740-55-1P | 254740-56-2P | 254740-57-3P |
| 254740-58-4P | 254740-59-5P | 254740-60-8P | 254740-61-9P | 254740-62-0P |
| 254740-63-1P | 254740-64-2P | 254740-65-3P | 254740-66-4P | 254740-67-5P |
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| 254741-27-0P | 254741-28-1P | 254741-30-5P | 254741-31-6P | 254741-32-7P |
| 254741-33-8P | 254741-34-9P | 254741-35-0P | 254741-36-1P | 254741-37-2P |
| 254741-38-3P | 254741-39-4P | 254741-40-7P | 254741-41-8P | 254741-42-9P |
| 254741-43-0P | 254741-44-1P | 254741-45-2P | 254741-46-3P | 254741-48-5P |
| 254741-50-9P | 254741-52-1P | 254741-54-3P | 254741-56-5P | 254741-58-7P |
| 254741-60-1P | 254741-62-3P | 254741-64-5P | 254741-66-7P | 254741-68-9P |
| 254741-70-3P | 254741-72-5P | 254741-74-7P | 254741-76-9P | 254741-78-1P |
| 254741-80-5P | 254741-82-7P | 254741-85-0P | 254741-87-2P | 254741-89-4P |
| 254741-91-8P | 254741-93-0P | 254741-95-2P | 254741-97-4P | 254741-99-6P |
| 254742-01-3P | 254742-03-5P | 254742-05-7P | 254742-06-8P | 254742-07-9P |
| 254742-08-0P | 254742-09-1P | 254742-10-4P | 254742-11-5P | 254742-12-6P |
| 254742-13-7P | 254742-14-8P | 254742-15-9P | 254742-16-0P | 254742-17-1P |
| 254742-18-2P | 254742-19-3P | 254742-20-6P | 254742-21-7P | 254742-22-8P |

L1 ANSWER 44 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
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254742-31-9P 254742-33-1P 254742-35-3P 254742-36-4P 254742-37-5P
254742-38-6P 254742-39-7P 254742-41-1P 254742-43-3P 254742-45-5P
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254742-54-6P 254742-56-8P 254742-58-0P 254742-60-4P 254742-62-6P
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254742-69-3P 254742-70-6P 254742-71-7P 254742-72-8P 254742-73-9P
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254742-80-8P 254742-81-9P 254742-82-0P 254742-83-1P 254742-84-2P
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254743-18-5P 254743-19-6P 254743-20-9P 254743-22-1P 254743-24-3P
254743-25-4P 254743-26-5P 254743-27-6P 254743-28-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT 254743-29-8P 254743-30-1P 254743-31-2P 254743-32-3P 254743-33-4P
254743-34-5P 254743-35-6P 254743-36-7P 254743-37-8P 254743-38-9P
254743-39-0P 254743-40-3P 254743-41-4P 254743-42-5P 254743-43-6P
254743-44-7P 254743-45-8P 254743-46-9P 254743-47-0P 254743-48-1P
254743-49-2P 254743-50-5P 254743-51-6P 254743-53-8P 254743-56-1P
254743-57-2P 254743-58-3P 254743-59-4P 254743-61-8P 254743-62-9P
254743-63-0P 254743-64-1P 254743-65-2P 254743-66-3P 254743-67-4P
254743-68-5P 254743-69-6P 254743-70-9P 254743-71-0P 254743-72-1P
254743-73-2P 254743-74-3P 254743-75-4P 254743-76-5P 254743-77-6P
254743-78-7P 254743-79-8P 254743-80-1P 254743-81-2P 254743-82-3P
254743-83-4P 254743-84-5P 254743-85-6P 254743-86-7P 254743-87-8P
254743-88-9P 254743-89-0P 254743-90-3P 254743-91-4P 254743-92-5P
254743-93-6P 254743-94-7P 254743-95-8P 254743-96-9P 254743-97-0P
254743-98-1P 254743-99-2P 254744-00-8P 254744-01-9P 254744-02-0P
254744-03-1P 254744-04-2P 254744-05-3P 254744-06-4P 254744-07-5P
254744-08-6P 254744-09-7P 254744-10-0P 254744-11-1P 254744-12-2P
254744-13-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT 56-12-2, 4-Aminobutyric acid, reactions 75-03-6, Iodoethane 78-09-1, Tetraethyl orthocarbonate 79-03-8, Propionyl chloride 79-44-7,

L1 ANSWER 44 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
Dimethylcarbamyl chloride 95-89-6, 2-Chloro-3,6-dimethylpyrazine 109-81-9, N-Methylethylenediamine 124-40-3, Dimethylamine, reactions 127-08-2, Potassium acetate 541-41-3, Ethyl chloroformate 543-27-1, Isobutyl chloroformate 589-15-1, 4-Bromobenzyl bromide 627-03-2, Ethoxyacetic acid 638-29-9, Valeryl chloride 676-58-4, Methylmagnesium chloride 680-15-9 767-00-0, 4-Cyanophenol 865-33-8, Potassium methoxide 873-75-6, 4-Bromobenzyl alcohol 1117-97-1, N-Methoxy-N-methylamine 1122-91-4, 4-Bromobenzaldehyde 1450-75-5 1530-32-1, Ethyltriphenylphosphonium bromide 1609-86-5, tert-Butyl isocyanate 2835-98-5 2905-25-1, 2-Bromobenzenesulfonyl chloride 3959-07-7, 4-Bromobenzylamine 4858-85-9, 2,3-Dichloropyrazine 5326-34-1, 4-Bromo-3-nitrotoluene 6228-47-3, Propyltriphenylphosphonium bromide 6482-24-2, 1-Bromo-2-methoxyethane 13734-41-3 14508-49-7, 2-Chloropyrazine 14678-02-5, 5-Amino-3-methylisoxazole 22059-22-9, Acetamide oxime 22884-29-3, Isobutyltriphenylphosphonium bromide 28466-21-9, 4-Amino-1,3,5-trimethylpyrazole 29006-02-8 33670-32-5, Methoxymethyltriphenylphosphonium bromide 34328-47-7 34841-06-0, 3-Bromo-4-methoxybenzaldehyde 40155-28-0, 2-Chloro-3-methoxypyrazine 41963-20-6, 4-Bromo-3-methylbenzonitrile 53553-14-3, Methyl 2-chloro-3-nitrobenzoate 53596-60-4 60421-23-0 74410-26-7 76513-69-4, 2-(Trimethylsilyl)ethoxymethyl chloride 78775-11-8 87199-17-5, 4-Formylphenylboronic acid 89464-87-9, 2-Amino-3-methoxy-5-methylpyrazine 98946-18-0, tert-Butyl 2,2,2-trichloroacetimidate 109072-25-5 120077-69-2 124750-49-8 125110-82-9, 4,4-Difluoropentanoic acid 133059-43-5 133240-06-9 138402-05-8 148547-19-7, Methyl 4-bromo-3-methylbenzoate 150691-04-6 151257-01-1 153039-15-7 160313-50-8 162647-41-8 167985-34-4 176961-13-0 195436-86-3 254746-77-5 254746-78-6 254746-79-7 254746-80-0 254746-81-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

IT 14847-51-9P 79047-47-5P 89003-95-2P 123652-98-2P 142031-67-2P
160313-48-4P 176961-30-1P 189762-06-9P 189762-08-1P 190197-86-5P
254744-14-4P 254744-15-5P 254744-16-6P 254744-17-7P 254744-18-8P
254744-19-9P 254744-20-2P 254744-21-3P 254744-22-4P 254744-23-5P
254744-24-6P 254744-25-7P 254744-26-8P 254744-27-9P 254744-28-0P
254744-29-1P 254744-30-4P 254744-31-5P 254744-32-6P 254744-33-7P
254744-34-8P 254744-35-9P 254744-36-0P 254744-37-1P 254744-38-2P
254744-39-3P 254744-40-6P 254744-41-7P 254744-42-8P 254744-43-9P
254744-44-0P 254744-45-1P 254744-46-2P 254744-47-3P 254744-48-4P
254744-49-5P 254744-50-8P 254744-51-9P 254744-52-0P 254744-53-1P
254744-54-2P 254744-55-3P 254744-56-4P 254744-58-6P 254744-60-0P
254744-63-3P 254744-65-5P 254744-68-8P 254744-70-2P 254744-73-5P
254744-78-0P 254744-81-5P 254744-84-8P 254744-86-0P 254744-87-1P
254744-90-6P 254744-91-7P 254744-95-1P 254744-98-4P 254745-00-1P

L1 ANSWER 44 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
254745-03-4P 254745-06-7P 254745-08-9P 254745-12-5P 254745-14-7P
254745-19-2P 254745-23-8P 254745-28-3P 254745-31-8P 254745-36-3P
254745-39-6P 254745-42-1P 254745-43-2P 254745-45-4P 254745-46-5P
254745-48-7P 254745-49-8P 254745-50-1P 254745-51-2P 254745-52-3P
254745-53-4P 254745-54-5P 254745-55-6P 254745-57-8P 254745-58-9P
254745-60-3P 254745-61-4P 254745-62-5P 254745-64-7P 254745-66-9P
254745-68-1P 254745-70-5P 254745-72-7P 254745-73-8P 254745-76-1P
254745-77-2P 254745-78-3P 254745-79-4P 254745-80-7P 254745-81-8P
254745-82-9P 254745-83-0P 254745-84-1P 254745-85-2P 254745-86-3P
254745-87-4P 254745-88-5P 254745-89-6P 254745-90-9P 254745-91-0P
254745-92-1P 254745-93-2P 254745-94-3P 254745-95-4P 254745-96-5P
254745-97-6P 254745-98-7P 254745-99-8P 254746-00-4P 254746-01-5P
254746-03-7P 254746-04-8P 254746-06-0P 254746-07-1P 254746-08-2P
254746-09-3P 254746-10-6P 254746-11-7P 254746-12-8P 254746-13-9P
254746-14-0P 254746-15-1P 254746-16-2P 254746-18-4P 254746-19-5P
254746-20-8P 254746-21-9P 254746-22-0P 254746-23-1P 254746-24-2P
254746-25-3P 254746-26-4P 254746-27-5P 254746-28-6P 254746-29-7P
254746-30-0P 254746-31-1P 254746-32-2P 254746-33-3P 254746-34-4P
254746-35-5P 254746-36-6P 254746-37-7P 254746-38-8P 254746-39-9P
254746-40-2P 254746-41-3P 254746-42-4P 254746-43-5P 254746-44-6P
254746-45-7P 254746-46-8P 254746-47-9P 254746-48-0P 254746-49-1P
254746-50-4P 254746-51-5P 254746-52-6P 254746-53-7P 254746-54-8P
254746-55-9P 254746-56-0P 254746-57-1P 254746-58-2P 254746-59-3P
254746-60-6P 254746-61-7P 254746-62-8P 254746-63-9P 254746-64-0P
254746-65-1P 254746-66-2P 254746-67-3P 254746-68-4P 254746-69-5P
254746-70-8P 254746-71-9P 254746-72-0P 254746-73-1P 254746-74-2P
254746-75-3P 254746-76-4P 254746-82-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-isoxazolyl biphenylsulfonamides and related compds. as dual **angiotensin II** and endothelin receptor antagonists)

L1 ANSWER 45 OF 123 CAPLUS COPYRIGHT 2003 ACS
1999:812115 Document No. 132:44367 Emerging treatments for hypertension: potential role for vasopeptidase inhibition. Weber, Michael (Department of Medicine, Brookdale Hospital Medical Center, Brooklyn, NY, 11212-3198, USA). American Journal of Hypertension, 12(11, Pt. 2), 139S-147S (English) 1999. CODEN: AJHYE6. ISSN: 0895-7061. Publisher: Elsevier Science Inc..

AB A review with 57 refs. Hypertension remains uncontrolled worldwide despite the availability of several classes of antihypertensive agents. There is an increased risk of serious cardiovascular, **cerebrovascular**, and renal events if the disease goes untreated or is poorly treated. Thus, the high incidence of hypertension coupled with its poor control make it imperative that more effective and well-tolerated treatments that exhibit target-organ protection be developed. Vasopeptidase inhibitors are a new class of cardiovascular agents that simultaneously inhibit neutral endopeptidase and angiotensin converting enzyme. They enhance peptides with vasodilatory and possibly organ-protective properties and also inhibit the prodn. of the vasoconstrictor **angiotensin II**. In preclin. studies, omapatrilat has shown blood pressure-lowering effects independent of renin status and has increased survival in an animal model of congestive heart failure. Human studies with omapatrilat, the most clin. advanced vasopeptidase inhibitor, administered orally once daily have demonstrated powerful dose-dependent redn. of systolic and diastolic blood pressures, regardless of age, race, or gender. Omapatrilat is particularly effective in lowering systolic blood pressure; this article summarizes data from recent clin. trials. This drug is well tolerated, with adverse effects comparable to those of currently available antihypertensive agents. Omapatrilat and other vasopeptidase inhibitors have potential applications in the treatment of hypertension, heart failure, and other cardiac and vascular disorders.

AB . . . remains uncontrolled worldwide despite the availability of several classes of antihypertensive agents. There is an increased risk of serious cardiovascular, **cerebrovascular**, and renal events if the disease goes untreated or is poorly treated. Thus, the high incidence of hypertension coupled with. . . angiotensin converting enzyme. They enhance peptides with vasodilatory and possibly organ-protective properties and also inhibit the prodn. of the vasoconstrictor **angiotensin II**. In preclin. studies, omapatrilat has shown blood pressure-lowering effects independent of renin status and has increased survival in an animal. . .

L1 ANSWER 46 OF 123 CAPLUS COPYRIGHT 2003 ACS
1999:811090 Document No. 132:30836 Preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination. Coniglio, Anthony A.; Platt, Francis R.; Blumenthal, Melvin S. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 9965500 A1 19991223, 20 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US12934 19990609. PRIORITY: US 1998-89650 19980617.

AB A method is provided for preventing a **cerebral infarction** by administering to a patient a combination of an ADP-receptor blocking antiplatelet drug, such as clopidogrel, in combination with an antihypertensive agent such as an angiotensin **II** antagonist (for example, irbesartan), an ACE inhibitor (for example, fosinopril) or a NEP/ACE inhibitor such as omapatrilat.

TI Preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination

AB A method is provided for preventing a **cerebral infarction** by administering to a patient a combination of an ADP-receptor blocking antiplatelet drug, such as clopidogrel, in combination with an antihypertensive agent such as an angiotensin **II** antagonist (for example, irbesartan), an ACE inhibitor (for example, fosinopril) or a NEP/ACE inhibitor such as omapatrilat.

ST **cerebral infarction** antiplatelet antihypertensive combination; ADP receptor antagonist **cerebral infarction**; ACE inhibitor **cerebral infarction**

IT Purinoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(P2T, antagonists; preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination)

IT Drug delivery systems
(capsules; preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination)

IT Brain, disease
(infarction; preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination)

IT Antihypertensives
Platelet aggregation inhibitors
(preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination)

L1 ANSWER 46 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT Drug delivery systems
(tablets; preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination)

IT 9015-82-1, Angiotensin-converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination)

IT 55142-85-3, Ticlopidine 62571-86-2, Captopril 75847-73-3, Enalapril 76547-98-3, Lisinopril 85441-61-8, Quinapril 86541-75-5, Benazepril 87333-19-5, Ramipril 87679-37-6, Trandolapril 98048-97-6, Fosinopril 113665-84-2, Clopidogrel 114798-26-4, Losartan 133040-01-4, Eprosartan 137862-53-4, Valsartan 138402-11-6, Irbesartan 139481-59-7, Candesartan 144701-48-4, Telmisartan 145733-36-4, Tasosartan 167305-00-2, Omapatrilat
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preventing **cerebral infarction** through administration of ADP-receptor antiplatelet and antihypertensive drugs in combination)

L1 ANSWER 47 OF 123 CAPLUS COPYRIGHT 2003 ACS
1999:704167 Document No. 132:59266 Emerging features of brain angiotensin receptors. Saavedra, J. M. (Section on Pharmacology, National Institute of Mental Health, Bethesda, MD, USA). Regulatory Peptides, 85(1), 31-45 (English) 1999. CODEN: REPPDY. ISSN: 0167-0115. Publisher: Elsevier Science Ireland Ltd..

AB A review with 73 refs. In mammalian brain, **angiotensin II** AT1 and AT2 receptor subtypes are apparently expressed only in neurons and not in glia. AT1 and AT2 receptor subtypes are sometimes closely assocd., but apparently expressed in different neurons. Brain AT1/AT2 interactions may occur in selective cases as inter-neuron cross talk. There are two AT1 isoforms in rodents, AT1A, which predominates, and AT1B. There are also important inter-species differences in receptor expression. Relative lack of amino acid conservation in the gerbil gAT1A receptor substantially decreases affinity for the AT1 antagonists. AT1 receptors are expressed in brain areas regulating autonomic and hormonal responses. AT1A receptors are heterogeneously regulated in a no. of exptl. conditions. In specific areas, AT1A receptors are not normally expressed, but are induced under influence of reproductive hormones in dopaminergic neurons. There are AT1 and AT2 receptors also in areas related to limbic, sensory and motor functions and their expression is developmentally regulated. A picture is emerging of widespread, neuronally localized, heterogeneously regulated, closely assocd. brain angiotensin receptor subtypes, modulating multiple functions including neuroendocrine and autonomic responses, stress, **cerebrovascular** flow, and perhaps brain maturation, neuronal plasticity, memory and behavior.

AB A review with 73 refs. In mammalian brain, **angiotensin II** AT1 and AT2 receptor subtypes are apparently expressed only in neurons and not in glia. AT1 and AT2 receptor subtypes. . . . widespread, neuronally localized, heterogeneously regulated, closely assocd. brain angiotensin receptor subtypes, modulating multiple functions including neuroendocrine and autonomic responses, stress, **cerebrovascular** flow, and perhaps brain maturation, neuronal plasticity, memory and behavior.

IT 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(brain angiotensin receptors)

L1 ANSWER 48 OF 123 CAPLUS COPYRIGHT 2003 ACS
1999:686140 Document No. 132:206425 Beneficial effect of renin-angiotensin system for maintaining blood pressure control following subarachnoid haemorrhage. Fassot, C.; Lambert, G.; Gaudet-Lambert, E.; Friberg, P.; Elghozi, J.-L. (CNRS UMR 8604, Laboratoire de Pharmacologie, Faculte de Medecine Necker, Paris, Fr.). Brain Research Bulletin, 50(2), 127-132 (English) 1999. CODEN: BRBUDU. ISSN: 0361-9230. Publisher: Elsevier Science Inc..

AB **Subarachnoid hemorrhage** is a serious condition often accompanied by delayed cerebral ischemia. Earlier reports have provided evidence suggesting a role for **angiotensin II** in the development of cerebral vasospasm following subarachnoid bleeding. The authors sought to examine the influence of **angiotensin II** blockade with losartan on blood pressure and survival in animals following exptl. **subarachnoid hemorrhage**, induced in conscious rats by injecting homologous blood via a catheter placed along the surface of the brain. The authors combined measurements of plasma renin activity with blood pressure recording in order to examine renin-angiotensin system activation following exptl. **subarachnoid hemorrhage**. Following subarachnoid injury an approx. threefold increase in plasma renin activity occurred (3.4 vs. 10.1 ng angiotensin I produced/mL/h). In animals treated with losartan (20 mg/kg) prior to the induction of **subarachnoid hemorrhage** blood pressure fell dramatically following the cerebral injury (124 vs. 94 mmHg), whereas blood pressure remained unchanged in control animals. Survival was markedly reduced in those animals treated with losartan. Given the pronounced decrease in blood pressure and impaired survival following **subarachnoid hemorrhage** in animals treated with losartan, it would appear that the acute activation of the renin-angiotensin system following this insult is in fact a desirable, compensatory response.

AB **Subarachnoid hemorrhage** is a serious condition often accompanied by delayed cerebral ischemia. Earlier reports have provided evidence suggesting a role for **angiotensin II** in the development of cerebral vasospasm following subarachnoid bleeding. The authors sought to examine the influence of **angiotensin II** blockade with losartan on blood pressure and survival in animals following exptl. **subarachnoid hemorrhage**, induced in conscious rats by injecting homologous blood via a catheter placed along the surface of the brain. The authors combined measurements of plasma renin activity with blood pressure recording in order to examine renin-angiotensin system activation following exptl. **subarachnoid hemorrhage**. Following subarachnoid injury an approx. threefold increase in plasma renin activity occurred (3.4 vs. 10.1 ng angiotensin I produced/mL/h). In animals treated with losartan (20 mg/kg) prior to the induction of **subarachnoid hemorrhage** blood pressure fell dramatically following the cerebral injury (124 vs. 94 mmHg), whereas blood pressure remained unchanged in control animals. . . . was markedly reduced in those animals treated with losartan. Given the pronounced decrease in blood pressure and impaired survival following **subarachnoid hemorrhage** in animals treated with losartan, it would appear that the acute activation of the

L1 ANSWER 48 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
renin-angiotensin system following this insult is. . .
ST renin angiotensin blood pressure **subarachnoid hemorrhage**
IT Blood pressure
(renin-angiotensin system in maintenance of blood pressure control following **subarachnoid hemorrhage**)
IT Blood plasma
(renin; renin-angiotensin system in maintenance of blood pressure control following **subarachnoid hemorrhage** in relation to)
IT Meninges
(**subarachnoid hemorrhage**; renin-angiotensin system in maintenance of blood pressure control following **subarachnoid hemorrhage**)
IT 9015-94-5, Renin, biological studies 11128-99-7, **Angiotensin II**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(renin-angiotensin system in maintenance of blood pressure control following **subarachnoid hemorrhage**)

L1 ANSWER 49 OF 123 CAPLUS COPYRIGHT 2003 ACS
1999:599251 Document No. 131:208400 Long-term potential of angiotensin receptor blockade for cardiovascular protection in hypertension: the VALUE trial. Julius, Stevo (Division of Hypertension, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA). Cardiology, 91(Suppl. 1), 8-13 (English) 1999. CODEN: CAGYAO. ISSN: 0008-6312. Publisher: S. Karger AG.
AB A review with 47 refs. The recent decrease of cardiovascular mortality in the USA is less pronounced than it has been in the preceding three decades. Elsewhere, cardiovascular mortality decreased and in some countries it increased. **Cerebrovascular** disease and ischemic heart disease were responsible for 21% of deaths recorded by the World Health Organization in 1990 and 1997, of which hypertension was estd. to be directly responsible for half of these deaths. Apart from blood pressure (BP) elevation, essential hypertension is frequently assocd. with factors that increase the risk of poor cardiovascular outcomes: insulin resistance/dyslipidemia, elevated angiotensin and norepinephrine, a tendency for hypercoagulability, platelet overactivity, tachycardia, vulnerability to arrhythmias, vascular hypertrophy, endothelial dysfunction, and left ventricular hypertrophy. Excess activation of the renin-angiotensin system, independent of BP elevation, contributes to these abnormalities. To achieve better results in the future, focus must be shifted from BP lowering to recognition of specific effects of drugs on these diverse pathophysiol. aspects of hypertension. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, which is evaluating the effect of valsartan (Diovan) vs. amlodipine, is a milestone in the effort to test whether newer compds. offer a better redn. of the cardiovascular consequences of hypertension, as well as good BP control. The hypothesis is that valsartan by antagonizing the neg. effects of angiotensin on smooth muscle cell growth, endothelial function, sympathetic overactivity, and coagulation, may have for the same degree of BP lowering, better protective effects than the leading calcium antagonist amlodipine.
AB . . . pronounced than it has been in the preceding three decades. Elsewhere, cardiovascular mortality decreased and in some countries it increased. **Cerebrovascular** disease and ischemic heart disease were responsible for 21% of deaths recorded by the World Health Organization in 1990 and. . .
IT Angiotensin receptor antagonists
(**angiotensin II**; long-term potential of angiotensin receptor blockade with valsartan for cardiovascular protection in hypertension in humans)

L1 ANSWER 50 OF 123 CAPLUS COPYRIGHT 2003 ACS
1999:414817 Document No. 131:209147 Angiotensin and cerebral blood flow. Saavedra, Juan M.; Nishimura, Yasuaki (Section on Pharmacology, National Institute of Mental Health, Bethesda, MD, 20892-1264, USA). Cellular and Molecular Neurobiology, 19(5), 553-573 (English) 1999. CODEN: CMNEDI. ISSN: 0272-4340. Publisher: Kluwer Academic/Plenum Publishers.
AB A review, with .apprx.110 refs. The authors discuss the following topics: (1) General properties of the cerebral circulation. (2) Cerebral blood flow autoregulation in hypertension, in stroke, and during the aging process. (3) The Angiotensin system. (4) Angiotensin receptor subtypes. (5) Angiotensin receptors and actions of **Angiotensin II** in the brain: interactions between the brain and circulating **Angiotensin II**. (6) The **cerebrovascular** Angiotensin system. (7) Effects of **Angiotensin II** on **cerebrovascular** reactivity. (8) Angiotensin and **cerebrovascular** flow. (9) Effects of therapeutic modulation of the **Angiotensin II** system on **cerebrovascular** regulation in health and disease.
AB . . . stroke, and during the aging process. (3) The Angiotensin system. (4) Angiotensin receptor subtypes. (5) Angiotensin receptors and actions of **Angiotensin II** in the brain: interactions between the brain and circulating **Angiotensin II**. (6) The **cerebrovascular** Angiotensin system. (7) Effects of **Angiotensin II** on **cerebrovascular** reactivity. (8) Angiotensin and **cerebrovascular** flow. (9) Effects of therapeutic modulation of the **Angiotensin II** system on **cerebrovascular** regulation in health and disease.
IT 1407-47-2, Angiotensin 11128-99-7, **Angiotensin-II**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(angiotensin and cerebral blood flow in relation to health and disease)

L1 ANSWER 51 OF 123 CAPLUS COPYRIGHT 2003 ACS
1999:56587 Document No. 130:104666 Protective effects of **angiotensin II** receptor antagonists on damaged target organs. Hiwada, Kunio (Sch. Med., Ehime Univ., Ehime, 791-02, Japan). Cardiac Practice, 10(1), 25-29 (Japanese) 1999. CODEN: CARPEM. ISSN: 0915-874X. Publisher: Medikaru Rebyusha.
AB A review with 14 refs., on effects of antihypertensive **angiotensin II** receptor antagonists on left ventricular hypertrophy, heart failure, **cerebrovascular** diseases, and renal failure.
TI Protective effects of **angiotensin II** receptor antagonists on damaged target organs
AB A review with 14 refs., on effects of antihypertensive **angiotensin II** receptor antagonists on left ventricular hypertrophy, heart failure, **cerebrovascular** diseases, and renal failure.
ST review **angiotensin II** receptor antagonist; antihypertensive angiotensin antagonist organ protection review
IT Angiotensin receptor antagonists
(**angiotensin II**; protective effects of **angiotensin II** receptor antagonists on damaged target organs)
IT Cytoprotective agents
(cardioprotective; protective effects of **angiotensin II** receptor antagonists on damaged target organs)
IT Antihypertensives
Brain, disease
Kidney, disease
(protective effects of **angiotensin II** receptor antagonists on damaged target organs)

L1 ANSWER 52 OF 123 CAPLUS COPYRIGHT 2003 ACS
1999:26515 Document No. 130:163577 AT1 receptors mediate **angiotensin II** uptake and transport by bovine brain microvessel endothelial cells in primary culture. Rose, Jayna M.; Audus, Kenneth L. (Department of Pharmaceutical Chemistry, The University of Kansas, School of Pharmacy, Lawrence, KS, USA). Journal of Cardiovascular Pharmacology, 33(1), 30-35 (English) 1999. CODEN: JCPCDT. ISSN: 0160-2446. Publisher: Lippincott Williams & Wilkins.

AB The endothelial lining of the blood-brain barrier tightly controls the distribution of peptide hormones between the central nervous system and the circulation. By using primary cultures of brain microvessel endothelial cells, an in vitro model of the blood-brain barrier, the authors report the uptake and transport of the octapeptide **angiotensin II** by a specific receptor population. With the **angiotensin II** antagonists losartan (AT1 specific) and PD 123,319 (AT2 specific), the authors showed that both the uptake and transport of **angiotensin II** were mediated by the AT1 receptor. Western blot anal. confirmed the existence of the AT1 receptor in the authors' cell-culture model. Rhodamine 123 studies also suggested that both **angiotensin II** antagonists, but not **angiotensin II**, were substrates for the P-glycoprotein efflux system, thus restricting the transport of these compds. These results suggest an AT1 receptor mediates uptake and transport of **angiotensin II** at the blood-brain barrier and may contribute to the regulation of **cerebrovascular** levels of the peptide.

TI AT1 receptors mediate **angiotensin II** uptake and transport by bovine brain microvessel endothelial cells in primary culture

AB . . . endothelial cells, an in vitro model of the blood-brain barrier, the authors report the uptake and transport of the octapeptide **angiotensin II** by a specific receptor population. With the **angiotensin II** antagonists losartan (AT1 specific) and PD 123,319 (AT2 specific), the authors showed that both the uptake and transport of **angiotensin II** were mediated by the AT1 receptor. Western blot anal. confirmed the existence of the AT1 receptor in the authors' cell-culture model. Rhodamine 123 studies also suggested that both **angiotensin II** antagonists, but not **angiotensin II**, were substrates for the P-glycoprotein efflux system, thus restricting the transport of these compds. These results suggest an AT1 receptor mediates uptake and transport of **angiotensin II** at the blood-brain barrier and may contribute to the regulation of **cerebrovascular** levels of the peptide.

ST AT1 receptor **angiotensin II** transport blood brain barrier

IT Blood-brain barrier
(AT1 receptors mediate **angiotensin II** uptake and transport by bovine brain microvessel endothelial cells in primary

L1 ANSWER 52 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
culture)

IT Angiotensin receptors
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(AT1; AT1 receptors mediate **angiotensin II** uptake and transport by bovine brain microvessel endothelial cells in primary culture)

IT Blood vessel
(microvessel, endothelium; AT1 receptors mediate **angiotensin II** uptake and transport by bovine brain microvessel endothelial cells in primary culture)

IT Biological transport
(uptake; AT1 receptors mediate **angiotensin II** uptake and transport by bovine brain microvessel endothelial cells in primary culture)

IT 11128-99-7, **Angiotensin-II**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(AT1 receptors mediate **angiotensin II** uptake and transport by bovine brain microvessel endothelial cells in primary culture)

L1 ANSWER 53 OF 123 CAPLUS COPYRIGHT 2003 ACS
1998:793244 Document No. 130:32608 Reserpine-diuretic combination in the treatment of hypertension. A review. Siepmann, Martin; Kirch, Wilhelm (Inst. Klinische Pharmakologie, Medizinische Fak., TU Dresden, Dresden, D-01307, Germany). Medizinische Klinik (Munich), 93(12), 733-737 (German) 1998. CODEN: MEKLA7. ISSN: 0723-5003. Publisher: Urban & Vogel GmbH.

AB A review with 57 refs. is given on combinations of reserpine with diuretics in treatment of hypertension. In combination with a diuretic even low doses of reserpine lower blood pressure sufficiently. Nasal constipation is the most frequently reported adverse event. Cardiovascular and **cerebrovascular** morbidity and mortality are decreased by reserpine-diuretic combinations. Reserpine-diuretic combinations cost less than Ca antagonists, ACE inhibitors, and **angiotensin II** receptor antagonists.

AB . . . even low doses of reserpine lower blood pressure sufficiently. Nasal constipation is the most frequently reported adverse event. Cardiovascular and **cerebrovascular** morbidity and mortality are decreased by reserpine-diuretic combinations. Reserpine-diuretic combinations cost less than Ca antagonists, ACE inhibitors, and **angiotensin II** receptor antagonists.

L1 ANSWER 54 OF 123 CAPLUS COPYRIGHT 2003 ACS
1998:788746 Document No. 130:52406 Substituted biphenyl isoxazole sulfonamides useful as endothelin antagonists. Murugesan, Natesan; Barrish, Joel C.; Spergel, Steven H. (Bristol-Myers Squibb Co., USA). U.S. US 5846990 A 19981208, 107 pp., Cont.-in-part of U.S. Ser. No. 754,715, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1997-799616 19970213. PRIORITY: US 1995-493331 19950724; US 1996-603975 19960220; US 1996-754715 19961121.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I inhibit the activity of endothelin (no data), and are useful as antihypertensives, etc. The symbols in I are defined as follows [one of X and Y = N, other = O; J = O, S, N, (un)substituted NH; K, L = N or C, provided that at least one is C; p = 0-2; R1-R4 (bound to ring C atoms) = H, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, aralkoxy, halo, OH, cyano, NO2, CHO, etc.; or R3R4 = (un)substituted alkylene or alkenylene; R5-R8 = groups similar to R1-R4, plus heterocyclyl, heterocyclyloxy, and others]. Over 280 synthetic examples are given. For instance, the MEM-protected, isoxazole-contg. bromide II [R = Br] was lithiated, treated with B(OPr-iso)3, and hydrolyzed to give 82% II [R = B(OH)2]. The latter was coupled with 2-(4-bromophenyl)oxazole using Pd(PPh3)4 catalyst (70%), followed by acidic deprotection of the MEM group (52%), to give title compd. III.

IT Angiotensin receptor antagonists
(**angiotensin II**, compns. addnl. contg.; prepn. of substituted biphenyl isoxazole sulfonamides as endothelin antagonists)

IT Meninges
(**subarachnoid hemorrhage**, treatment; prepn. of substituted biphenyl isoxazole sulfonamides as endothelin antagonists)

L1 ANSWER 55 OF 123 CAPLUS COPYRIGHT 2003 ACS

1998:726129 Document No. 130:90770 Responsiveness of human infant cerebral arteries to sympathetic nerve stimulation and vasoactive agents. Bevan, Rosemary; Dodge, John; Nichols, Patricia; Poseno, Tina; Vijayakumaran, Edathoot; Wellman, Terry; Bevan, John A. (Totman Laboratory for Cerebrovascular Research, Department of Pharmacology, College of Medicine, University of Vermont, Burlington, VT, 05405, USA). Pediatric Research, 44(5), 730-739 (English) 1998. CODEN: PEREBL. ISSN: 0031-3998. Publisher: Lippincott Williams & Wilkins.

AB Responses of segments of basilar and middle cerebral arteries of eight human infants to activation of perivascular nerves and to vasoactive drugs were studied using a resistance artery myograph. The infants ages ranged from 23 wk of gestation to 34 postnatal days. Neurogenic vasoconstriction occurred in all segments and at 8 Hz was 12.7% of tissue max. and was blocked by phentolamine (10-6 M). There was no evidence of a neurogenic dilator response. Catecholamine histofluorescence was seen in nerves in the adventitia at all ages studied. Norepinephrine ED50 was 7.6 .times. 10-7 M, and its max. effect was 43.1% of tissue max. Both neural and norepinephrine responses were greater than those of the proximal parts of adult human middle cerebral arteries obtained postmortem and surgically removed adult human pial arteries. Electron microscopy demonstrated that neural d. at the adventitiomedial junction in the infant vessels was greater than in the pial arteries. Constrictor responses to serotonin and prostaglandin F2.alpha. were minimal in the two infants of 23 and 24 wk of gestation but were clearly present in the older infants. Histamine and acetylcholine were potent vasodilators. Indomethacin potentiated agonist-induced contraction. In a limited no. of trials **angiotensin II**, neuropeptide Y, caused contraction and bradykinin, relaxation. It is concluded that there is a quant. similarity between the studied responses of infant cerebral artery segments and human pial arteries of similar diam. However, sympathetic nerves may potentially play a more important role in the regulation of **cerebrovascular** tone in the infant compared with the adult, and during the gestational period examd. these vessels possess an indomethacin-sensitive system that buffers agonist tone.

AB . . . in the older infants. Histamine and acetylcholine were potent vasodilators. Indomethacin potentiated agonist-induced contraction. In a limited no. of trials **angiotensin II**, neuropeptide Y, caused contraction and bradykinin, relaxation. It is concluded that there is a quant. similarity between the studied responses. . . human pial arteries of similar diam. However, sympathetic nerves may potentially play a more important role in the regulation of **cerebrovascular** tone in the infant compared with the adult, and during the gestational period examd. these vessels possess an indomethacin-sensitive system. . .

IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine 51-45-6, Histamine, biological studies 51-84-3, Acetylcholine, biological studies 58-82-2, Bradykinin 551-11-1, PGF2.alpha.

L1 ANSWER 55 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

11128-99-7, **Angiotensin-II** 82785-45-3, Neuropeptide Y

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(human infant cerebral artery responsiveness to sympathetic nerve stimulation and vasoactive agents)

L1 ANSWER 56 OF 123 CAPLUS COPYRIGHT 2003 ACS

1998:633323 Document No. 130:33061 The valsartan antihypertensive long-term use evaluation (VALUE) trial of cardiovascular events in hypertension. Rationale and design. Mann, Jessica; Julius, Stevo (Department of Internal Medicine, Division of Hypertension, University of Michigan Medical Center, Ann Arbor, MI, 48109-0356, USA). Blood Pressure, 7(3), 176-183 (English) 1998. CODEN: BLPREG. ISSN: 0803-7051. Publisher: Scandinavian University Press.

AB Essential hypertension is a major Public Health issue. Although the no. of treated hypertensive patients has increased, only 25% of treated patients have their blood pressure levels under control. The benefit of treating hypertension has been proven, but cardiovascular morbidity and mortality rates remain high. The ideal antihypertensive drug should not only normalize blood pressure levels, but also reduce the assocd. cardiovascular morbidity and mortality rates. The role of **angiotensin II** in systemic hypertension and its complications has been recently redefined. The potent trophic effects of **angiotensin II** on blood vessels and on cardiac cells have been well demonstrated, esp. the role of **angiotensin II** in left ventricular hypertrophy, vascular hypertrophy, endothelial dysfunction, and congestive heart failure. Of all ongoing mortality and morbidity trials in systemic hypertension, VALUE (Valsartan Antihypertensive Long-term Use Evaluation) is the only one comparing an **angiotensin II** antagonist (valsartan) with a third-generation calcium channel blocker (amlodipine). A review with 55 refs. The main hypothesis of the VALUE trial is that, for an equiv. decrease in blood pressure, valsartan will be more effective than amlodipine in decreasing cardiac mortality and morbidity. VALUE is a prospective, multinational, multicenter, double-blind, randomized, active-controlled, 2-arm parallel group comparison with a response-dependent dose titrn. scheme. VALUE involves 14 400 patients in over 30 countries, who will be followed for 4 yr or until 1450 patients experience a primary endpoint. The population to be included in VALUE consists of hypertensive men and women, aged 50 yr or older, and at a relatively high risk of sustaining a cardiovascular event. The high risk profile is defined taking into account age, gender, and a list of cardiovascular risk factors and disease factors. Risk factors are cigarette smoking, hypercholesterolemia, diabetes mellitus, uncomplicated left ventricular hypertrophy, proteinuria, and high serum creatinine. Disease factors include documented history of myocardial infarction, peripheral vascular disease, stroke or **transient ischemic attack**, or the presence of left ventricular hypertrophy with strain on the ECG. A unique feature of VALUE is the assessment of the predictive power of this cardiovascular risk factor scale in a large population of treated hypertensive patients. The trial started on 10 Sept. 1997.

AB . . . should not only normalize blood pressure levels, but also reduce the assocd. cardiovascular morbidity and mortality rates. The role of **angiotensin II** in systemic hypertension and its complications has been recently redefined. The potent trophic effects of **angiotensin II** on blood vessels and on cardiac cells have been well demonstrated, esp. the role of **angiotensin II** in left ventricular hypertrophy, vascular hypertrophy, endothelial dysfunction, and congestive heart failure. Of all ongoing mortality and morbidity trials in systemic hypertension, VALUE (Valsartan Antihypertensive Long-term Use Evaluation) is the only one comparing an **angiotensin II** antagonist (valsartan) with a third-generation calcium channel blocker (amlodipine). A review with 55 refs. The main hypothesis of the VALUE. . . ventricular hypertrophy, proteinuria, and high serum creatinine. Disease factors include documented history of myocardial infarction, peripheral vascular disease, stroke or **transient ischemic attack**, or the presence of left ventricular hypertrophy with strain on the ECG. A unique feature of VALUE is the assessment. . .

L1 ANSWER 56 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

L1 ANSWER 57 OF 123 CAPLUS COPYRIGHT 2003 ACS
1998:323144 Document No. 129:12752 Treating Alzheimer's disease with folate, vitamin B12, organic nitrates, and ACE inhibitors or **angiotensin II** antagonists. Smith, Anthony David; Jobst, Kim Anthony (Bristol-Myers Squibb Co., USA). PCT Int. Appl. WO 9819690 A1 19980514, 48 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US20021 19971104. PRIORITY: US 1996-30642 19961106.

AB A method is provided for treating occlusive vascular disease or Alzheimer's disease, wherein the patient has at least moderately elevated blood levels of homocysteine and at least moderately reduced blood levels of folate and vitamin B12, wherein the patient is treated with folic acid, a folate or a deriv. thereof, and optionally vitamin B12, and optionally an org. nitrate such as isosorbide mononitrate or dinitrate, or an ACE inhibitor or an **angiotensin II** antagonist, or a NEP/ACE inhibitor or a combination of two or more of the above.

TI Treating Alzheimer's disease with folate, vitamin B12, organic nitrates, and ACE inhibitors or **angiotensin II** antagonists

AB . . . optionally vitamin B12, and optionally an org. nitrate such as isosorbide mononitrate or dinitrate, or an ACE inhibitor or an **angiotensin II** antagonist, or a NEP/ACE inhibitor or a combination of two or more of the above.

IT Brain, disease
(**cerebrovascular**, occlusive; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Nerve
(degeneration; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Mental disorder
(dementia, multi-infarct; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Mental disorder
(dementia, vascular, Binswanger's disease; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Mental disorder
(dementia, vascular; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Brain

L1 ANSWER 57 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT 55-63-0, Nitroglycerin 58-05-9, Leucovorin 87-33-2, Isosorbide dinitrate 107-43-7, Betaine 134-35-0 135-16-0 2800-34-2, 10-Formyltetrahydrofolate 3432-99-3 4033-27-6 8059-24-3, Vitamin b6 10360-12-0 16051-77-7, Isosorbide mononitrate 62571-86-2, Captopril 72973-85-4 75847-73-3, Enalapril 76547-98-3, Lisinopril 80830-42-8, Fentiapril 85441-61-8, Quinapril 86541-75-5, Benazepril 87333-19-5, Ramipril 98048-97-6, Fosinopril 103775-10-6, Moexipril 114798-26-4, Losartan 138402-11-6, Irbesartan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

L1 ANSWER 57 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
(homocysteine in; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Artery, disease
(intermittent claudication; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Brain, disease
(ischemia, transient; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Brain, disease
(ischemia; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Mental disorder
(senile psychosis; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Brain, disease
(stroke; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT Alzheimer's disease
(treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT 6027-13-0, Homocysteine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(donors; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT 9015-82-1 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

IT 59-30-3, Folic acid, biological studies 68-19-9, Vitamin b12
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(treating Alzheimer's disease with folate, vitamin B12, org. nitrates, and ACE inhibitors or **angiotensin II** antagonists)

L1 ANSWER 58 OF 123 CAPLUS COPYRIGHT 2003 ACS
1998:121175 Document No. 128:269079 Constrictor responses of the rat basilar artery during diabetes mellitus. Mayhan, William G. (Department of Physiology and Biophysics, University of Nebraska Medical Center, Omaha, NE, 68198-4575, USA). Brain Research, 783(2), 326-331 (English) 1998. CODEN: BRREAP. ISSN: 0006-8993. Publisher: Elsevier Science B.V.,

AB Diabetes mellitus produces abnormalities of the endothelium and impairs endothelium-dependent dilatation of large and small cerebral blood vessels. However, the effect of diabetes mellitus on cerebral vasoconstriction and the modulatory influence of nitric oxide on cerebral vasoconstriction is unclear. Thus, the first goal of this study was to examine the effect of diabetes mellitus on constrictor responses of the basilar artery in vivo. The authors' second goal was to examine a potential role for nitric oxide in modulating constrictor responses of the basilar artery. A craniotomy was performed over the ventral medulla to expose the basilar artery. The diam. of the basilar artery was measured using intravital microscopy in nondiabetic and diabetic (3-4 mo after injection of streptozotocin; 50-60 mg/kg i.p.) rats in response to **angiotensin II**, arginine vasopressin, endothelin-1, and the thromboxane analog, U-46619. Topical application of **angiotensin II** (10 and 100 nM) produced only minimal changes in diam. of the basilar artery which were similar in nondiabetic and diabetic rats. Arginine vasopressin (0.1 and 1.0 nM), endothelin-1 (10 and 50 nM), and U-46619 (10 and 100 nM) produced marked dose-related constriction of the basilar artery which was similar in both nondiabetic and diabetic rats. Next, whether the synthesis/release of nitric oxide played a role in constriction of the basilar artery in response to the agonists was examd. L-NMMA (1.0 .mu.M) did not alter constrictor responses of the basilar artery in nondiabetic and diabetic rats. Thus, responses of the basilar artery to important vasoactive agonists are not altered by diabetes mellitus. In addn., the synthesis/release of nitric oxide probably does not modulates constrictor responses of the basilar artery to **angiotensin II**, arginine vasopressin, endothelin-1 and U-46619. Preservation of vasoconstrictor responses, coupled with impaired vasodilator responses, may contribute to the pathogenesis of **cerebrovascular** abnormalities assocd. with diabetes mellitus.

AB . . . using intravital microscopy in nondiabetic and diabetic (3-4 mo after injection of streptozotocin; 50-60 mg/kg i.p.) rats in response to **angiotensin II**, arginine vasopressin, endothelin-1, and the thromboxane analog, U-46619. Topical application of **angiotensin II** (10 and 100 nM) produced only minimal changes in diam. of the basilar artery which were similar in nondiabetic and. . . diabetes mellitus. In addn., the synthesis/release of nitric oxide probably does not modulates constrictor responses of the basilar artery to **angiotensin II**, arginine vasopressin, endothelin-1 and U-46619. Preservation of vasoconstrictor responses, coupled with impaired vasodilator responses, may contribute to the pathogenesis of **cerebrovascular** abnormalities assocd. with diabetes mellitus.

IT 113-79-1, Arginine vasopressin 11128-99-7, **Angiotensin II** 123626-67-5, Endothelin-1

L1 ANSWER 58 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(modulating role of nitric oxide in cerebral vasoconstriction in health and diabetes mellitus)

L1 ANSWER 59 OF 123 CAPLUS COPYRIGHT 2003 ACS
1998:99809 Document No. 128:203768 Serial observation of plasma endothelin RAS renin-angiotensin system and calcitonin gene-related peptide with **cerebral infarction**. Zhou, Wu; Yu, Burun (Department of Neurology, The Affiliated Tongji Hospital, Tongji Medical University, Wuhan, 430030, Peop. Rep. China). Tongji Yike Daxue Xuebao, 26(3), 195-198 (Chinese) 1997. CODEN: TYDXEP. ISSN: 0258-2090. Publisher: Tongji Yike Daxue.
AB The relation of **cerebral infarction** (CI) and its complications with plasma endothelins (P-ET), **angiotensin II** (p-A II), aldosterone (P-ALD) and calcitonin gene-related peptide (CGRP) were studied. 40 Patients with CI were divided into 3 groups : **cerebral infarction** group, atherosclerosis group and normal controls. P-ET, P-A II, P-ALD and P-CGRP levels of CI patients were detd. on 3rd day, 10-14th days and 25-28th days after onset. also for atherosclerosis patients and normal controls. The P-ET, P-A II and P-ALD levels of CI patients in total process were higher than those of the normal controls, but the P- CGRP levels of CI patients in total process were higher than those of the normal controls, but the P-CGRP levels were lower. The P-ET and P-A II levels of CI patients with hypertension were higher than those without hypertension, but the P-CGRP levels were lower. The P-ET, P-A II levels of CI patients with diabetes were higher than those without diabetes. The P-ET, P-A II and P-CGRP levels on 3rd day after onset of CI patients in serious state of the illness were higher than those in light and moderate states. The results suggests that (1) **cerebral infarction** is correlated with P-ET, P-A II, P-ALD and P-CGRP, (2) hypertension is correlated with P-ET, P-A II and P-CGRP, (3) diabetes is correlated with ET and A II, and (4) in patients on 3rd day after onset the P- ET, p-A II and P-CGRP levels can roughly reflect the state of the illness.
TI Serial observation of plasma endothelin RAS renin-angiotensin system and calcitonin gene-related peptide with **cerebral infarction**
AB The relation of **cerebral infarction** (CI) and its complications with plasma endothelins (P-ET), **angiotensin II** (p-A II), aldosterone (P-ALD) and calcitonin gene-related peptide (CGRP) were studied. 40 Patients with CI were divided into 3 groups : **cerebral infarction** group, atherosclerosis group and normal controls. P-ET, P-A II, P-ALD and P-CGRP levels of CI patients were detd. on 3rd. . . . in serious state of the illness were higher than those in light and moderate states. The results suggests that (1) **cerebral infarction** is correlated with P-ET, P-A II, P-ALD and P-CGRP, (2) hypertension is correlated with P-ET, P-A II and P-CGRP, (3). . . .
ST endothelin **angiotensin II** aldosterone **cerebral infarction**; calcitonin gene related peptide **cerebral infarction**
IT Brain, disease
(infarction; plasma endothelin, aldosterone, renin-angiotensin system

L1 ANSWER 59 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
and calcitonin gene-related peptide assoc. with **cerebral infarction**)
IT Diabetes mellitus
Hypertension
(plasma endothelin, aldosterone, renin-angiotensin system and calcitonin gene-related peptide assoc. with **cerebral infarction**)
IT 52-39-1, Aldosterone 11128-99-7, **Angiotensin II** 83652-28-2, Calcitonin gene related peptide 116243-73-3, Endothelin
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(plasma endothelin, aldosterone, renin-angiotensin system and calcitonin gene-related peptide assoc. with **cerebral infarction**)

L1 ANSWER 60 OF 123 CAPLUS COPYRIGHT 2003 ACS
1998:98322 Document No. 128:167435 Preparation of heterocyclyl-substituted biphenylsulfonamide as endothelin antagonists. Murugesan, Natesan; Barrish, Joel C.; Stein, Philip D. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 9804260 A1 19980205, 85 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US12180 19970715. PRIORITY: US 1996-692869 19960725.
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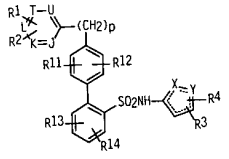
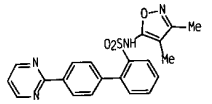


I



II

AB Compds. of formula (I; R1 and R2 are directly bonded to a ring carbon and are each independently hydrogen, alkyl or alkoxy, hydroxyl, halo, or amino; one of X and Y is N and the other is O; R3 and R4 are each directly bonded to a ring carbon and are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl or aralkoxy, any of which may be substituted or R3 and R4 together may also be alkylene or alkenylene, either of which may be substituted, completing a 4- to 8-membered satd., unsatd. or arom. ring together with the carbon atoms to which they are attached; R11 - R14 are each independently are hydrogen alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, aralkoxy, or heterocyclyl, any of which may be substituted, halo, OH, cyano, NO2, CHO, CO2H, etc.; J, K, L, T, and U are each independently N or C, provided that at least one is N, and at most two are N; and when only one of J, K, L, T, and U is N, the

L1 ANSWER 60 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
N may be substituted with O- so that N-oxide is formed), which inhibit the activity of endothelin (no data), are prepd. Also claimed is a method for treating endothelin-related disorders in a mammal, such as (1) hypertension, (2) pulmonary hypertension, (3) renal, glomerular, or mesangial cell disorders, (4) endotoxemia, (5) ischemia, (6) atherosclerosis, (7) restenosis, (8) **subarachnoid hemorrhage**, (9) prostatic hypertrophy, and (10) congestive heart failure, and a method for inhibiting cell growth. Said compd. I is used in combination with at least one **angiotensin II** receptor antagonist, renin inhibitor, angiotensin converting enzyme (ACE) inhibitor, or a dual neutral endopeptidase-ACE inhibitor for treating the endothelin-related disorder. A pharmaceutical compn. for the treating the endothelin-related disorders comprises said compd. optionally in combination with at least one **angiotensin II** receptor antagonist, renin inhibitor, angiotensin converting enzyme (ACE) inhibitor, or a dual neutral endopeptidase-ACE inhibitor. Thus, 2-(4-bromophenyl)pyrimidine is coupled with 2-borono-N-(3,4-dimethyl-5-isoxazolyl)-N-[(2-methoxyethoxy)methyl]benzenesulfonamide in the presence of (Ph3P)4Pd in a mixt. of toluene, 2 M aq. Na2CO3, and 95% ethanol under reflux for 1.5 h to give the title compd., N-isoxazolylpyrimidinylbiphenyl sulfonamide (II).

AB . . . hypertension, (2) pulmonary hypertension, (3) renal, glomerular, or mesangial cell disorders, (4) endotoxemia, (5) ischemia, (6) atherosclerosis, (7) restenosis, (8) **subarachnoid hemorrhage**, (9) prostatic hypertrophy, and (10) congestive heart failure, and a method for inhibiting cell growth. Said compd. I is used in combination with at least one **angiotensin II** receptor antagonist, renin inhibitor, angiotensin converting enzyme (ACE) inhibitor, or a dual neutral endopeptidase-ACE inhibitor for treating the endothelin-related disorder. A pharmaceutical compn. for the treating the endothelin-related disorders comprises said compd. optionally in combination with at least one **angiotensin II** receptor antagonist, renin inhibitor, angiotensin converting enzyme (ACE) inhibitor, or a dual neutral endopeptidase-ACE inhibitor. Thus, 2-(4-bromophenyl)pyrimidine is coupled with. . .

ST . . . disorder treatment isoxazolylbiphenylsulfonamide; mesangial cell disorder treatment isoxazolylbiphenylsulfonamide; endotoxemia treatment isoxazolylbiphenylsulfonamide; ischemia treatment isoxazolylbiphenylsulfonamide; atherosclerosis treatment isoxazolylbiphenylsulfonamide; restenosis treatment isoxazolylbiphenylsulfonamide; **subarachnoid hemorrhage** treatment isoxazolylbiphenylsulfonamide; prostatic hypertrophy treatment isoxazolylbiphenylsulfonamide; congestive heart failure treatment isoxazolylbiphenylsulfonamide; cell growth inhibitor isoxazolylbiphenylsulfonamide

IT Angiotensin receptor antagonists
(**angiotensin II**; prepn. of heterocyclyl-substituted biphenylsulfonamide as endothelin antagonists for treating endothelin-related disorders)

IT Meninges
(**subarachnoid hemorrhage**; prepn. of heterocyclyl-substituted biphenylsulfonamide as endothelin antagonists for treating endothelin-related disorders)

L1 ANSWER 61 OF 123 CAPLUS COPYRIGHT 2003 ACS
1998:91962 Document No. 128:213005 Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. Rocha, Ricardo; Chander, Praveen N.; Khanna, Kavita; Zuckerman, Andrea; Stier, Charles T., Jr. (Dept. of Pharmacology, New York Medical College, Valhalla, NY, 10595, USA). Hypertension, 31(1, Pt. 2), 451-458 (English) 1998. CODEN: HPRTDN. ISSN: 0194-911X. Publisher: Williams & Wilkins.

AB Chronic treatment of saline-drinking stroke-prone spontaneously hypertensive rats (SHRSP) with agents that interfere with the formation or actions of **angiotensin II** prevents the development of stroke and renal vascular damage. **Angiotensin II**, in addn. to its direct vascular effects, stimulates the synthesis and release of aldosterone. To assess the role of aldosterone in the development of pathol. changes in these rats, time-release pellets contg. 200 mg of the mineralocorticoid receptor antagonist, spironolactone, were implanted into 14 SHRSP at 7.5 wk of age. Over the period of study (3-4 wk), systolic blood pressure was not different between implanted and control groups. Spironolactone did not enhance water and electrolyte excretion. All placebo-treated SHRSP developed marked proteinuria (150 mg/day), whereas in spironolactone-treated SHRSP, urinary protein excretion (UPE) averaged 39 mg/day. In a 2nd study to assess effects on survival, 6 SHRSP received spironolactone (10 mg/kg/day) and 6 received vehicle. All but 1 of the control rats displayed signs of stroke and died by 16 wk of age, while the spironolactone-treated SHRSP remained asymptomatic through 19 wk of age. At 16 wk of age, spironolactone-treated SHRSP were severely hypertensive (247 mm Hg), yet UPE remained at baseline levels. In contrast, preterminal UPE averaged 136 mg/day in control rats. In both studies, histopathol. examn. revealed a marked protective effect of spironolactone against the development of malignant nephrosclerotic and **cerebrovascular** lesions. These observations indicate a vascular and end-organ protective effect of spironolactone in the absence of lowered blood pressure in saline-drinking SHRSP and are consistent with a major role for mineralocorticoids as hormonal mediators of vascular injury.

AB Chronic treatment of saline-drinking stroke-prone spontaneously hypertensive rats (SHRSP) with agents that interfere with the formation or actions of **angiotensin II** prevents the development of stroke and renal vascular damage. **Angiotensin II**, in addn. to its direct vascular effects, stimulates the synthesis and release of aldosterone. To assess the role of aldosterone. . . rats. In both studies, histopathol. examn. revealed a marked protective effect of spironolactone against the development of malignant nephrosclerotic and **cerebrovascular** lesions. These observations indicate a vascular and end-organ protective effect of spironolactone in the absence of lowered blood pressure in. . .

L1 ANSWER 62 OF 123 CAPLUS COPYRIGHT 2003 ACS
1997:684304 Document No. 127:351205 Pharmaceutical compositions containing **angiotensin II** antagonists and additional agents for treatment of **angiotensin II**-mediated diseases. Tamura, Norikazu; Sohda, Takashi; Ikeda, Hitoshi (Takeda Chemical Industries, Ltd., Japan; Tamura, Norikazu; Sohda, Takashi; Ikeda, Hitoshi). PCT Int. Appl., WO 9737688 A2 19971016, 61 pp. DESIGNATED STATES: W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-JP1149 19970403. PRIORITY: JP 1996-83917 19960405.

AB To provide a pharmaceutical compn. which performs a remarkable effect with a relatively decreased dosage and with less side effects, a pharmaceutical compn. was formulated by combination of an **angiotensin II**-mediated compd. or a salt thereof with at least one species of a compd. having the activity of increasing insulin sensitivity, a compd. having the activity of improving postprandial hyperglycemia in diabetes mellitus, an indane deriv. having the activity of inhibiting angiotensin-converting enzyme, a pyridine deriv. having the activity of inhibiting HMG-Co A reductase or salts thereof. A capsule for treatment of arteriosclerosis was formulated contg. 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-1H-benzimidazole-7-carboxylic acid 1, 5-[4-[-2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione 30, lactose 69, microcryst. cellulose 70, and Mg stearate 10 mg.

TI Pharmaceutical compositions containing **angiotensin II** antagonists and additional agents for treatment of **angiotensin II**-mediated diseases

AB . . . effect with a relatively decreased dosage and with less side effects, a pharmaceutical compn. was formulated by combination of an **angiotensin II**-mediated compd. or a salt thereof with at least one species of a compd. having the activity of increasing insulin sensitivity. . . .

IT Heart, disease
(angina pectoris; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)

IT Angiotensin receptor antagonists
(**angiotensin II**; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)

IT Drug delivery systems
(capsules; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)

IT Schizophrenia
(catatonia; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)

IT Nervous system

L1 ANSWER 62 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
(central, disease; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Brain, disease
(**cerebrovascular**; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Artery
Artery
(coronary, angioplasty, obstruction after; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Artery
Artery
(coronary, bypass surgery, vascular reobstruction after; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II** -mediated diseases)
IT Mental disorder
(depression; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Kidney, disease
(diabetic nephropathy; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Heart, disease
Kidney, disease
Organ, animal
Organ, animal
(failure; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Kidney, disease
(glomerulonephritis; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Kidney, disease
(glomerulosclerosis; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Lipids, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(hyperlipidemia; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Blood vessel, disease
(hypertrophy; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Heart, disease
(infarction; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Drug delivery systems
(injections; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Vein
(insufficiency; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Heart, disease
(ischemia; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Kidney, disease
(nephritis; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Mental disorder
(neurosis; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Aldosteronism
Alzheimer's disease
Amnesia
Aneurysm
Antiarteriosclerotics
Anticoagulants
Antidiabetic agents
Antihypertensives
Anxiolytics
Glaucoma (disease)
Ischemia
(pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Memory, biological
(retention defect; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Connective tissue
(scleroderma; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Mental disorder
(senile psychosis; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT Drug delivery systems
(tablets; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT 9015-82-1, Angiotensin-converting enzyme 9028-35-7, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT 83435-66-9 83480-29-9 111025-46-8 139481-59-7 145040-37-5 145599-86-6 147403-03-0 178610-08-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)
IT 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmaceutical compns. contg. **angiotensin II** antagonists and addnl. agents for treatment of **angiotensin II**-mediated diseases)

L1 ANSWER 63 OF 123 CAPLUS COPYRIGHT 2003 ACS
1997:568440 Document No. 127:229432 Preventive effect of iganidipine on renal and cerebral injuries in salt-induced hypertension. Shirahase, Hiroaki; Wada, Katsuo; Uehara, Yoshio; Nakamura, Shohei; Ichikawa, Atsuko (Research Laboratories, Kyoto Pharmaceutical Industries, Ltd., Kyoto, 604, Japan). American Journal of Hypertension, 10(8), 869-878 (English) 1997. CODEN: AJHYE6. ISSN: 0895-7061. Publisher: Elsevier.
AB Iganidipine, a new water-sol. calcium antagonist, was administered at a nonhypotensive dose (NHD) of 0.3 mg/kg/day, a moderate-hypotensive dose (MHD) of 1.0 mg/kg/day, and a sustained-hypotensive dose (SHD) of 3.0 mg/kg/day to Dahl salt-sensitive (Dahl-S) rats fed a high-salt diet for 8 wk. The effects on survival, and on renal and cerebral injuries, were then examd. Iganidipine completely prevented hypertensive death at the SHD and tended to increase the survival at the NHD and MHD. Iganidipine reduced glomerulosclerosis and renal arterial and tubular injuries in a dose-dependent manner. Iganidipine at the SHD, but not NHD or MHD, improved plasma creatinine, serum urea nitrogen, and glomerular filtration rate. Iganidipine at all doses examd. increased the urinary prostaglandin (PG) I2 and PGE2, but not PGF2.alpha. or thromboxane B2, and decreased plasma **angiotensin II (AII)** level and renin activity. The renal glomerular, tubular, and arterial injuries were significantly correlated with blood pressure (r = 0.56 to 0.80) and plasma **AII** level (r = 0.50 to 0.71) but not with urinary prostanoids. Iganidipine also reduced the incidence of **cerebral infarction**. The infarction area was slightly and significantly correlated with urinary PGI2 (r = 0.42) and PGE2 (r = 0.41) but not with blood pressure or plasma **AII**. In conclusion, iganidipine prevented renal and cerebral injuries in Dahl-S rats. In addn. to the reduced blood pressure, the redn. of plasma **AII** and the increase of vasodilatory prostanoids may also partially contribute to the renal and cerebral protective effects of iganidipine.
AB . . . all doses examd. increased the urinary prostaglandin (PG) I2 and PGE2, but not PGF2.alpha. or thromboxane B2, and decreased plasma **angiotensin II (AII)** level and renin activity. The renal glomerular, tubular, and arterial injuries were significantly correlated with blood pressure (r = 0.56 to 0.80) and plasma **AII** level (r = 0.50 to 0.71) but not with urinary prostanoids. Iganidipine also reduced the incidence of **cerebral infarction**. The infarction area was slightly and significantly correlated with urinary PGI2 (r = 0.42) and PGE2 (r = 0.41) but not with blood pressure or plasma **AII**. In conclusion, iganidipine prevented renal and cerebral injuries in Dahl-S rats. In addn. to the reduced blood pressure, the redn. of plasma **AII** and the increase of vasodilatory prostanoids may also partially contribute to the renal and cerebral protective effects of iganidipine.
IT 363-24-6, Prostaglandin E2 551-11-1, Prostaglandin F2.alpha. 9015-94-5, Renin, biological studies 11128-99-7, **Angiotensin II** 35121-78-9, Prostaglandin I2 54397-85-2, Thromboxane B2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preventive effect of iganidipine on renal and cerebral injuries in salt-induced hypertension)

L1 ANSWER 63 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

L1 ANSWER 64 OF 123 CAPLUS COPYRIGHT 2003 ACS

1997:557640 Document No. 127:248103 Substituted biphenyl isoxazole sulfonamides useful as endothelin antagonists. Murugesan, Natesan; Barrish, Joel C.; Spergel, Steven H. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 9729748 A1 19970821, 325 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US3956 19970220. PRIORITY: US 1996-603975 19960220; US 1996-754715 19961121; US 1997-799616 19970213.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I inhibit the activity of endothelin (no data), and are useful as antihypertensives, etc. The symbols in I are defined as follows [one of X and Y = N, other = O; J = O, S, N, (un)substituted NH; K, L = N or C, provided that at least one is C; p = 0-2; R1-R4 (bound to ring C atoms) = H, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aryloxy, aralkyl, aralkoxy, halo, OH, cyano, NO2, CHO, etc.; or R3R4 = (un)substituted alkylene or alkenylene; R5-R8 = groups similar to R1-R4, plus heterocyclyl, heterocyclyloxy, and others]. Over 280 synthetic examples are given. For instance, the MEM-protected, isoxazole-contg. bromide II [R = Br] was lithiated, treated with B(OPr-iso)3, and hydrolyzed to give 82% II [R = B(OH)2]. The latter was coupled with 2-(4-bromophenyl)oxazole using Pd(PPh3)4 catalyst (70%), followed by acidic deprotection of the MEM group (52%), to give title compd. III.

IT Angiotensin receptor antagonists
(**angiotensin II**, compns. addnl. contg.; prepn. of substituted biphenyl isoxazole sulfonamides as endothelin antagonists)

IT Meninges
(**subarachnoid hemorrhage**, treatment; prepn. of substituted biphenyl isoxazole sulfonamides as endothelin antagonists)

L1 ANSWER 65 OF 123 CAPLUS COPYRIGHT 2003 ACS

1997:426953 Document No. 127:116899 **Angiotensin II** receptor antagonists: potential in elderly patients with cardiovascular disease. Burrell, Louise M.; Johnston, Colin I. (Department of Medicine, University of Melbourne, Austin, Australia). Drugs & Aging, 10(6), 421-434 (English) 1997. CODEN: DRAGE6. ISSN: 1170-229X. Publisher: Adis.

AB A review with 65 refs. Raised blood pressure in the elderly is not a normal consequences of aging, but is a major risk factor for cardiovascular disease. Cardiac and **cerebrovascular** disease account for >50% of deaths among people aged >65 yr. Because the percentage of elderly people in most populations is rising, blood pressure control in this group is becoming increasingly important. Several large intervention studies in the elderly have demonstrated that antihypertensive medication reduces cardiovascular morbidity and mortality. In addn., the abs. benefits of blood pressure redn. are higher in elderly compared with younger patients. ACE inhibitors are effective and well tolerated in the treatment of hypertension in the elderly. Their success led to interest in alternative ways of blocking the renin angiotensin system, and the subsequent development of **angiotensin II (AII)** receptor antagonists. Losartan was the first drug in this class to become com. available. Since then, valsartan has been launched in some markets and others are likely to be launched in the near future. Losartan is effective in the treatment of essential hypertension and has a low incidence of adverse effects. First-dose hypotension is very uncommon and, at the present time, cough does not appear to be an adverse effect of these drugs, although long term tolerability studies are needed to confirm this. Angioedema, a rare but life-threatening adverse effect of ACE inhibitors, has also been assocd. with losartan. Current data suggest that **AII** receptor antagonists are effective in elderly hypertensive patients, although further data are needed to confirm these findings. At present, **AII** receptor antagonists are likely to be used in hypertensive patients who are intolerant of ACE inhibitors, although this may change with the availability of long term tolerability and clin. outcomes data.

TI **Angiotensin II** receptor antagonists: potential in elderly patients with cardiovascular disease

AB . . . the elderly is not a normal consequences of aging, but is a major risk factor for cardiovascular disease. Cardiac and **cerebrovascular** disease account for >50% of deaths among people aged >65 yr. Because the percentage of elderly people in most populations. . . elderly. Their success led to interest in alternative ways of blocking the renin angiotensin system, and the subsequent development of **angiotensin II (AII)** receptor antagonists. Losartan was the first drug in this class to become com. available. Since then, valsartan has been launched. . . Angioedema, a rare but life-threatening adverse effect of ACE inhibitors, has also been assocd. with losartan. Current data suggest that **AII** receptor antagonists are effective in elderly hypertensive patients, although further data are needed to confirm these findings. At present, **AII** receptor antagonists are likely to be used in hypertensive patients who are intolerant of ACE inhibitors, although this may change.

L1 ANSWER 65 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

. .

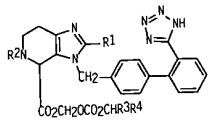
IT Hypertension
(**angiotensin II** receptor antagonists for elderly patients with cardiovascular disease)

IT Angiotensin receptor antagonists
(**angiotensin II**; **angiotensin II** receptor antagonists for elderly patients with cardiovascular disease)

IT Aging, animal
(elderly; **angiotensin II** receptor antagonists for elderly patients with cardiovascular disease)

L1 ANSWER 66 OF 123 CAPLUS COPYRIGHT 2003 ACS
1997:405439 Document No. 127:39817 Pharmaceutical compositions containing imidazopyridines as **angiotensin II** antagonists.
Sekine, Yasuo; Kawanishi, Eiki; Narita, Hiroshi; Hashimoto, Yoshihiro; Mizobe, Masakazu (Tanabe Seiyaku Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 09110691 A2 19970428 Heisei, 7 pp. (Japanese). CODEN: JKXXAF.
APPLICATION: JP 1995-267560 19951017.

GI



I

AB Pharmaceutical compns., useful for treatment and/or prevention of hypertension, nephritis, diabetic nephritis, primary aldosteronemia, atherosclerosis, dementia, cerebral circulation disorder, chronic heart failure, and angina pectoris, contain imidazopyridines I (R1, R3, R4 = lower alkyl; R2 = lower alkanoyl; R3R4 may form C3-6 alkylene) or their pharmacol. acceptable salts as active ingredients. I (R1 = Pr, R2 = Ac, R3 = R4 = Et) HCl salt (II) at 0.3 mg/kg i.d. suppressed 61.6% **angiotensin II**-induced hypertension in dogs. LD50 of II was >1800 mg/kg p.o. in rats.

TI Pharmaceutical compositions containing imidazopyridines as **angiotensin II** antagonists

AB . . . (R1 = Pr, R2 = Ac, R3 = R4 = Et) HCl salt (II) at 0.3 mg/kg i.d. suppressed 61.6% **angiotensin II**-induced hypertension in dogs. LD50 of II was >1800 mg/kg p.o. in rats.

ST antihypertensive imidazopyridine **angiotensin II** antagonist

IT Antiarteriosclerotics
(antiatherosclerotics; prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT Brain, disease
(**cerebrovascular**; prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT Mental disorder
(dementia; prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

L1 ANSWER 66 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT Kidney, disease
(diabetic nephropathy; prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT Heart, disease
(failure, chronic; prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT Kidney, disease
(nephritis; prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT Antianginal agents
Antihypertensives
(prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT 52-39-1, Aldosterone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metab. disorder; prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT 190602-73-4P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT 173307-01-2P 173307-02-3P 190602-72-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT 35180-01-9P 40510-86-9P 166813-55-4P 173307-04-5P 173307-05-6P 173307-07-8P 176310-42-2P 190602-74-5P 190602-75-6P
RL: PNU (Preparation, unclassified); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

IT 76-83-5, Trityl chloride 79-22-1, Methyl chloroformate 584-02-1, 3-Pentanol 7791-25-5, Sulfuryl chloride 173307-10-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of imidazopyridines as **angiotensin II** antagonists for treatment of cardiovascular diseases)

L1 ANSWER 67 OF 123 CAPLUS COPYRIGHT 2003 ACS
1997:384287 Document No. 127:1228 Angiotensin IV and analogs as regulators of fibrinolysis. Vaughan, Douglas E.; Harding, Joseph W. (Brigham and Women's Hospital, USA; Washington State University Research Foundation). PCT Int. Appl. WO 9716201 A1 19970509, 64 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US13804 19960827. PRIORITY: US 1995-550174 19951030.

AB Angiotensin IV (VAL-TYR-ILE-HIS-PRO-PHE), a degrdn. product of **angiotensin II** previously thought to be inactive. interacts directly with endothelial cells to induce expression of PAI-1 and thereby to inhibit clot lysis attributable to endogenous t-PA. Moreover, angiotensin IV does not effect substantial physiol. changes (vasoconstriction, increased blood pressure, etc.) characteristic of **angiotensin II**. Fibrinolysis is promoted by reducing the amt. or the effect of angiotensin IV. Fibrinolysis is inhibited by providing enhanced angiotensin IV. Methods of screening candidates for antagonizing angiotensin IV are also disclosed.

AB Angiotensin IV (VAL-TYR-ILE-HIS-PRO-PHE), a degrdn. product of **angiotensin II** previously thought to be inactive. interacts directly with endothelial cells to induce expression of PAI-1 and thereby to inhibit clot. . . attributable to endogenous t-PA. Moreover, angiotensin IV does not effect substantial physiol. changes (vasoconstriction, increased blood pressure, etc.) characteristic of **angiotensin II**. Fibrinolysis is promoted by reducing the amt. or the effect of angiotensin IV. Fibrinolysis is inhibited by providing enhanced angiotensin. . .

IT Brain, disease
(**cerebrovascular**; angiotensin IV and analogs as promoters or inhibitors of fibrinolysis in a variety of medical conditions)

IT 11128-99-7, **Angiotensin II**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(use of compds. that inhibit the conversion of **angiotensin II** to angiotensin IV as promoters of fibrinolysis)

L1 ANSWER 68 OF 123 CAPLUS COPYRIGHT 2003 ACS
1996:750082 Document No. 126:26596 Effects of losartan on cerebral arteries in stroke-prone spontaneously hypertensive rats. Vacher, Elisabeth; Richer, Christine; Giudicelli, Jean-Francois (Department de Pharmacologie, Faculte de Medecine, Le Kremlin-Bicetre, 94276, Fr.). Journal of Hypertension, 14(11), 1341-1348 (English) 1996. CODEN: JOHYD3. ISSN: 0263-6352. Publisher: Rapid Science Publishers.
AB The objective of this study was to investigate in young salt-loaded stroke-prone spontaneously hypertensive rats (SHR-SP) the effects of a long-term administration of the **angiotensin II** AT1 receptor antagonist losartan [1 mg/kg (L1) and 10 mg/kg (L10) per day at 5-20 wk of age] on the structural and functional characteristics of the middle cerebral artery. Morphol. measurements and isometric tension recordings (myograph, contractile responses to KCl and serotonin, and relaxant responses to bradykinin and sodium nitroprusside) were performed on isolated vessels from randomly selected control and losartan-treated SHR-SP and age-matched Wistar-Kyoto (WKY) rats killed at ages 6-7, 10-11, and 16-17 wk. Whereas all control SHR-SP had died within 18 wk of being born, losartan at both doses afforded full protection against stroke and mortality. Losartan limited malignant hypertension development dose-dependently. Age-related increases in cerebral arterial wall thickness and wall:lumen ratio were not affected (L1) or limited slightly (L10) by losartan. In control SHR-SP, contractile responses of cerebral arteries to agonists decreased with aging and stroke occurrence and were significantly smaller than those of age-matched WKY rat arteries. Losartan limited the **cerebrovascular** contractility impairment dose-dependently in SHR-SP but did not affect the WKY rat cerebral artery contractility. In addn., losartan limited the age-related alteration of the endothelium-dependent relaxation of cerebral arteries obsd. in control SHR-SP dose-dependently. Thus, in SHR-SP, losartan prevented stroke and improved the cerebral artery's smooth muscle and endothelial cell functions, which are altered during aging and impaired even more dramatically by stroke occurrence.
AB . . . study was to investigate in young salt-loaded stroke-prone spontaneously hypertensive rats (SHR-SP) the effects of a long-term administration of the **angiotensin II** AT1 receptor antagonist losartan [1 mg/kg (L1) and 10 mg/kg (L10) per day at 5-20 wk of age] on the. . . decreased with aging and stroke occurrence and were significantly smaller than those of age-matched WKY rat arteries. Losartan limited the **cerebrovascular** contractility impairment dose-dependently in SHR-SP but did not affect the WKY rat cerebral artery contractility. In addn., losartan limited the. . .

L1 ANSWER 69 OF 123 CAPLUS COPYRIGHT 2003 ACS
1996:319527 Document No. 125:25882 ME3221, a surmountable angiotensin AT1-receptor antagonist, prevents hypertensive complications in aged stroke-prone spontaneously hypertensive rats. Nagura, Jun; Hui, Chen; Yamamoto, Mikio; Yasuda, Sumie; Abe, Mitsuhiro; Hachisu, Mitsugu; Konno, Fukio (Pharmaceutical Res. Center, Meiji Seika Kaisha, Ltd., Yokohama, 222, Japan). Japanese Journal of Pharmacology, 71(1), 39-49 (English) 1996. CODEN: JJPAAZ. ISSN: 0021-5198. Publisher: Japanese Pharmacological Society.
AB The protective effects of ME3221, 3-methoxy-2,6-dimethyl-4-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methoxy]pyridine, on aged (32-wk-old) stroke-prone spontaneously hypertensive rats (SHRSP) were studied following long-term (for 8 mo) oral administration. At a dose of 10 mg/kg/day, ME3221 suppressed the mortality and the hypertensive complications obsd. in control SHRSP: **cerebral apoplexy** (hemorrhage, and spongeform and malacia in the cerebral cortex), increased proteinuria, and total N-acetyl-.beta.-D-glucosaminidase activity, and cardiac hypertrophy and pleural effusion. The protective activity of ME3221, a surmountable angiotensin AT1-receptor antagonist, was comparable to losartan, an insurmountable AT1-antagonist, and also to enalapril, an angiotensin-converting enzyme inhibitor. In addn, ME3221 reduced the systolic blood pressure more effectively than the two ref. drugs.
AB . . . oral administration. At a dose of 10 mg/kg/day, ME3221 suppressed the mortality and the hypertensive complications obsd. in control SHRSP: **cerebral apoplexy** (hemorrhage, and spongeform and malacia in the cerebral cortex), increased proteinuria, and total N-acetyl-.beta.-D-glucosaminidase activity, and cardiac hypertrophy and pleural. . .
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**angiotensin II** AT1, ME3221, an angiotensin AT1-receptor antagonist, prevents hypertensive complications in aged stroke-prone spontaneously hypertensive rats)

L1 ANSWER 70 OF 123 CAPLUS COPYRIGHT 2003 ACS
1996:282552 Document No. 124:332358 Protective effects of ME3221 on hypertensive complications and lifespan in salt-loaded stroke-prone spontaneously hypertensive rats. Nagura, Jun; Yamamoto, Mikio; Hui, Chen; Yasuda, Sumie; Hachisu, Mitsugu; Konno, Fukio (Pharmaceutical Res. Center, Meiji Seika Kaisha Ltd., Yokohama, Japan). Clinical and Experimental Pharmacology and Physiology, 23(3), 229-235 (English) 1996. CODEN: CEXPB9. ISSN: 0305-1870. Publisher: Blackwell.
AB A comparison was made on the protective effects of the following: ME3221, a competitive angiotensin AT1 receptor antagonist; losartan, in which a major active metabolite is a non-competitive angiotensin AT1 receptor antagonist; and enalapril, an angiotensin-converting enzyme inhibitor, using the salt-loaded stroke-prone spontaneously hypertensive rats (SHRSP). SHRSP received orally ME3221 (3 and 10 mg/kg per day), losartan (10 mg/kg per day) and enalapril (10 mg/kg per day) from the 6th to the 20th week of age. All the control rats showed rapid elevation of systolic blood pressure (SBP), accompanied by hypertensive complications, and died by 15 wk of age. ME3221, losartan and enalapril suppressed the elevation of SBP in the salt-loaded SHRSP to a comparable degree. ME3221 and losartan increased the survival rate to >90%, and diminished hypertensive complications such as **cerebral apoplexy** (stroke), renal injury (increased proteinuria, and total N-acetyl-.beta.-D-glucosaminidase activity) and heart failure (cardiac hypertrophy and pleural effusion). Competitive (ME3221) and non-competitive (losartan) angiotensin AT1 receptor antagonists showed comparable efficacy against the complications and mortality of the salt-loaded SHRSP; both were more potent than enalapril in the protective effect.
AB . . . SHRSP to a comparable degree. ME3221 and losartan increased the survival rate to >90%, and diminished hypertensive complications such as **cerebral apoplexy** (stroke), renal injury (increased proteinuria, and total N-acetyl-.beta.-D-glucosaminidase activity) and heart failure (cardiac hypertrophy and pleural effusion). Competitive (ME3221) and. . .
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**angiotensin II** AT1, protective effects of ME3221, losartan, and enalapril on hypertensive complications and lifespan in salt-loaded stroke-prone spontaneously hypertensive rats)

L1 ANSWER 71 OF 123 CAPLUS COPYRIGHT 2003 ACS
1996:32028 Document No. 124:77283 The role of angiotensin receptor subtypes in **cerebrovascular** regulation in the rat. Naeveri, Liisa (Institute of Biomedicine, University of Helsinki, Helsinki, Finland). Acta Physiologica Scandinavica, Supplementum, 155(630), 48pp (English) 1995. CODEN: APSSAD. ISSN: 0302-2994. Publisher: Blackwell.
AB The present studies were conducted to examine the roles of **angiotensin II**, angiotensin IV, and the angiotensin receptor subtypes in the cerebral circulation. The effects of **angiotensin II**, the selective AT1 receptor antagonist losartan, and the selective AT2 receptor ligands, PD 123319 and CGP 42112, on cerebral blood flow autoregulation, were studied during increases and decreases in blood pressure in normotensive rats. Cerebrocortical blood flow was measured by laser-Doppler flowmetry, while systemic blood pressure was either increased by phenylephrine infusion, or decreased by controlled hemorrhage. The effects of **angiotensin II**, and AT1 and AT2 receptor ligands on the contractility of rat anterior cerebral artery in vitro, were studied using cannulated, perfused vessel segments. The effect of angiotensin IV on cerebral blood flow after exptl. **subarachnoid hemorrhage**, and possible involvement of nitric oxide, was studied in rat. **Subarachnoid hemorrhage** was simulated by injecting 0.3 mL arterial blood into the cisterna magna, while cerebral blood flow was measured by laser-Doppler flowmetry. The main findings in the present studies were that **angiotensin II**, the AT1 antagonist losartan, and the AT2 ligands PD 123319 and CGP 42112, shifted the cerebral blood flow autoregulatory range towards higher blood pressures. PD 123319 and CGP 42112 acted as AT2 receptor agonists. In vitro, **angiotensin II** elicited an AT1 receptor mediated contraction of rat anterior cerebral artery. Angiotensin IV was able to reverse the acute CBF redn. after **subarachnoid hemorrhage**. No evidence was found to support the involvement of nitric oxide in this response. In conclusion, there is strong evidence supporting a role for the AT2 receptor in the regulation of cerebral circulation. The role of the AT1 receptor is questionable, and the losartan induced autoregulatory shift is possibly mediated indirectly through AT2 receptor stimulation. Although AT1 receptors mediate the **angiotensin II** induced contraction of rat anterior cerebral artery in vitro, this effect does not explain the effect of losartan on CBF autoregulation. Angiotensin IV increases cerebral blood flow after exptl. **subarachnoid hemorrhage** possibly by dilating cerebral vessels through stimulation of the AT4 receptor.
TI The role of angiotensin receptor subtypes in **cerebrovascular** regulation in the rat
AB The present studies were conducted to examine the roles of **angiotensin II**, angiotensin IV, and the angiotensin receptor subtypes in the cerebral circulation. The effects of **angiotensin II**, the selective AT1 receptor antagonist losartan, and the selective AT2 receptor ligands, PD 123319 and CGP 42112, on cerebral blood. . . laser-Doppler flowmetry, while systemic blood pressure was either increased by phenylephrine infusion, or decreased by controlled hemorrhage. The effects of **angiotensin II**.

L1 ANSWER 71 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
and AT1 and AT2 receptor ligands on the contractility of rat anterior cerebral artery in vitro, were studied using cannulated, perfused vessel segments. The effect of angiotensin IV on cerebral blood flow after exptl. **subarachnoid hemorrhage**, and possible involvement of nitric oxide, was studied in rat. **Subarachnoid hemorrhage** was simulated by injecting 0.3 mL arterial blood into the cisterna magna, while cerebral blood flow was measured by laser-Doppler flowmetry. The main findings in the present studies were that **angiotensin II**, the AT1 antagonist losartan, and the AT2 ligands PD 123319 and CGP 42112, shifted the cerebral blood flow autoregulatory range towards higher blood pressures. PD 123319 and CGP 42112 acted as AT2 receptor agonists. In vitro, **angiotensin II** elicited an AT1 receptor mediated contraction of rat anterior cerebral artery. Angiotensin IV was able to reverse the acute CBF redn. after **subarachnoid hemorrhage**. No evidence was found to support the involvement of nitric oxide in this response. In conclusion, there is strong evidence. . . questionable, and the losartan induced autoregulatory shift is possibly mediated indirectly through AT2 receptor stimulation. Although AT1 receptors mediate the **angiotensin II** induced contraction of rat anterior cerebral artery in vitro, this effect does not explain the effect of losartan on CBF autoregulation. Angiotensin IV increases cerebral blood flow after exptl. **subarachnoid hemorrhage** possibly by dilating cerebral vessels through stimulation of the AT4 receptor.

IT Hypertension
Hypotension
(angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT Circulation
(brain; angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT Brain
(circulation; angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**angiotensin II** AT1, angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**angiotensin II** AT2, angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT Artery
(cerebral, angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

L1 ANSWER 71 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT Meninges
(diseases, **subarachnoid hemorrhage**, angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT 4474-91-3, Human **angiotensin II** 114798-26-4, Losartan 127060-75-7, CGP 42112 130663-39-7, PD 123319
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT 23025-68-5, Human angiotensin IV
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT 10102-43-9, Nitric oxide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

IT 11128-99-7, **Angiotensin II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(angiotensin receptor subtype role in **cerebrovascular** regulation in the rat)

L1 ANSWER 72 OF 123 CAPLUS COPYRIGHT 2003 ACS
1995:865874 Document No. 123:282166 Hypertensive **cerebrovascular** disease and the renin-angiotensin system. Rossi, GianPaolo; Rossi, Alberto; Sacchetto, Alfredo; Pavan, Edoardo; Pessina, Achille C. (University Hospital, University Padua, Padua, 35126, Italy). Stroke (Dallas), 26(9), 1700-6 (English) 1995. CODEN: SJCCA7. ISSN: 0039-2499. Publisher: American Heart Association.

AB A review with 99 refs. Arterial hypertension is the leading cause of cardiovascular disease and is assocd. with an increased risk of stroke and heart attack. These complications have been largely attributed to the remodeling of the arterial wall, including accelerated atherosclerosis occurring in hypertensive patients. Although the risk of hemorrhagic stroke seems to be directly related to the level of blood pressure elevation, no such tight relation has been found between blood pressure levels and atherosclerosis. This observation has led to the concept that a no. of genetic, humoral, and cellular factors may be involved in atherogenesis in hypertensive patients. The exptl. and clin. evidence concerning the role of the renin-angiotensin system in cardiovascular remodeling and atherogenesis of the **cerebrovascular** bed as well as the data supporting an assocn. between **angiotensin II** and thrombotic stroke are examd. The contribution of the renin-angiotensin system to the pathogenesis of accelerated carotid artery atherosclerosis and particularly of **cerebrovascular** disease remains to be definitively proven. However, the bulk of exptl. and clin. data are consistent with the hypothesis that the renin-angiotensin system may play a detrimental role.

TI Hypertensive **cerebrovascular** disease and the renin-angiotensin system

AB . . . patients. The exptl. and clin. evidence concerning the role of the renin-angiotensin system in cardiovascular remodeling and atherogenesis of the **cerebrovascular** bed as well as the data supporting an assocn. between **angiotensin II** and thrombotic stroke are examd. The contribution of the renin-angiotensin system to the pathogenesis of accelerated carotid artery atherosclerosis and particularly of **cerebrovascular** disease remains to be definitively proven. However, the bulk of exptl. and clin. data are consistent with the hypothesis that. . .

ST review hypertension **cerebrovascular** disease renin angiotensin

IT Brain, disease
(**cerebrovascular**, hypertensive; renin-angiotensin system in)

IT 9015-94-5, Renin, biological studies 11128-99-7, **Angiotensin II**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(renin-angiotensin system in hypertensive cardiovascular disease)

L1 ANSWER 73 OF 123 CAPLUS COPYRIGHT 2003 ACS
1995:809800 Document No. 123:189350 Suppression of cerebral vasodilation with endothelin-1. Kaito, Nobuyoshi; Onoue, Hisashi; Abe, Toshiaki (Dep. of Neurosurgery, Jikei Univ. School of Medicine, Tokyo, 105, Japan). Peptides (Tarrytown, New York), 16(6), 1127-32 (English) 1995. CODEN: PPTDD5. ISSN: 0196-9781. Publisher: Elsevier.

AB The authors investigated the effect of endothelin-1 on relaxation responses induced by vasodilator substances in canine middle cerebral arteries to better understand regulation of **cerebrovascular** tone and its potential impact on mechanism of cerebral vasospasm. Endothelin-1 elicited concn.-dependent contractions in helical strips of canine cerebral arteries (EC50; 4.62 .times. 10-9 M). Pretreatment with 10-9M endothelin-1 significantly reduced endothelium-dependent relaxation elicited by substance P and endothelium-independent relaxations by nitroglycerin, prostaglandin I2, and KCl. Although endothelin-1 in a lower concn. (10-10M) did not affect these endothelium-independent relaxations, it did inhibit endothelium-dependent relaxation caused by substance P. As low concn. (10-10M) of endothelin-1 also significantly reduced endothelium-dependent relaxation of canine mesenteric arteries induced by acetylcholine. Other vasoconstrictor peptides such as **angiotensin-II** and vasopressin did not inhibit endothelium-dependent and -independent relaxations. These results indicate that endothelin-1 not only produces cerebral vasoconstriction but also interferes with vasodilator mechanisms and that endothelium-dependent vasodilation is more sensitive to the inhibitory effect of endothelin-1 than endothelium-independent vasodilation.

AB . . . effect of endothelin-1 on relaxation responses induced by vasodilator substances in canine middle cerebral arteries to better understand regulation of **cerebrovascular** tone and its potential impact on mechanism of cerebral vasospasm. Endothelin-1 elicited concn.-dependent contractions in helical strips of canine cerebral. . . (10-10M) of endothelin-1 also significantly reduced endothelium-dependent relaxation of canine mesenteric arteries induced by acetylcholine. Other vasoconstrictor peptides such as **angiotensin-II** and vasopressin did not inhibit endothelium-dependent and -independent relaxations. These results indicate that endothelin-1 not only produces cerebral vasoconstriction but. . .

IT 51-84-3, Acetylcholine, biological studies 113-79-1 7440-09-7, Potassium, biological studies 11128-99-7, **Angiotensin-II** 33507-63-0, Substance P 35121-78-9, Prostaglandin I2 123626-67-5, Endothelin-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(endothelin-1 suppression of cerebral vasodilation)

L1 ANSWER 74 OF 123 CAPLUS COPYRIGHT 2003 ACS

1995:761477 Document No. 123:169625 preparation of biphenylylmethyltetrazole derivatives as **angiotensin II** antagonists. Hirata, Terukage; Sakae, Nobuya; Tamura, Koichi; Okuhira, Masayasu; Amano, Hirotaka; Yokomoto, Masaharu; Nomiyama, Jun (Wakunaga Seiyaku K. K., Japan). PCT Int. Appl. WO 9404516 A1 19940303, 122 pp. DESIGNATED STATES: W: CA, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1993-JP1134 19930811. PRIORITY: JP 1992-214094 19920811; JP 1993-68706 19930326.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I: A = O, Q1 (wherein R1 = H, alkyl, cycloalkyl, (un)substituted Ph, aralkyl, acyl, etc.; X = O, S; Y = N, :CR2; Z = O, N, :CR3 wherein R2, R3 = H, halo, (un)substituted alkyl, (protected) carboxyl, cycloalkyl, alkenyl, alkoxy, etc., R2 or R3 with adjacent C atoms may form benzo); B = cyano, (protected) carboxyl, tetrazol-5-yl], effective **angiotensin II** antagonists useful in treating hypertension and such other circulatory diseases as **cerebral apoplexy**, are prepd. II was added to a suspension of NaH (55% in oil) in DMF with stirring, followed by a soln. of tetrazole deriv. III in DMF, the mixt. was stirred at room temp., the concd. filtrate was stirred with 10% HCl in dioxane to give IV, which showed an IC50 of 8.0 x 10-9 M against **angiotensin II** receptor binding. I also lowered blood pressure by 27.6-41.2% at 3 mg/kg orally in rats.

TI preparation of biphenylylmethyltetrazole derivatives as **angiotensin II** antagonists

AB . . . alkenyl, alkoxy, etc., R2 or R3 with adjacent C atoms may form benzo); B = cyano, (protected) carboxyl, tetrazol-5-yl], effective **angiotensin II** antagonists useful in treating hypertension and such other circulatory diseases as **cerebral apoplexy**, are prepd. II was added to a suspension of NaH (55% in oil) in DMF with stirring, followed by a. . . was stirred with 10% HCl in dioxane to give IV, which showed an IC50 of 8.0 x 10-9 M against **angiotensin II** receptor binding. I also lowered blood pressure by 27.6-41.2% at 3 mg/kg orally in rats.

ST biphenylylmethyltetrazole prepn **angiotensin II** antagonist; antihypertensive biphenylylmethyltetrazole prepn; apoplexy treatment biphenylylmethyltetrazole prepn; circulatory disease biphenylylmethyltetrazole prepn

IT Antihypertensives
(prepn. of heterocyclyl biphenyls as **angiotensin II** antagonists)

L1 ANSWER 74 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

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| 167006-61-3P | 167006-62-4P | 167006-63-5P | 167006-64-6P | 167006-65-7P |
| 167006-66-8P | 167006-67-9P | 167006-68-0P | 167006-69-1P | 167006-70-4P |
| 167006-71-5P | 167006-72-6P | 167006-73-7P | 167006-74-8P | 167006-75-9P |
| 167006-76-0P | 167006-77-1P | 167006-78-2P | 167006-79-3P | 167006-80-6P |
| 167006-81-7P | 167006-82-8P | 167006-83-9P | 167006-84-0P | 167006-85-1P |
| 167006-86-2P | 167006-87-3P | 167006-88-4P | 167006-89-5P | 167006-90-8P |
| 167006-91-9P | 167006-92-0P | 167006-93-1P | 167006-94-2P | 167006-95-3P |
| 167006-96-4P | 167006-97-5P | 167006-98-6P | 167006-99-7P | 167007-00-3P |
| 167007-01-4P | 167007-02-5P | 167007-03-6P | 167007-04-7P | 167007-05-8P |
| 167007-06-9P | 167007-07-0P | 167007-08-1P | 167007-09-2P | 167007-10-5P |
| 167007-11-6P | 167007-12-7P | 167007-13-8P | 167007-14-9P | 167007-15-0P |
| 167007-16-1P | 167007-17-2P | 167007-18-3P | 167007-19-4P | |

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclyl biphenyls as **angiotensin II** antagonists)

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| 167007-20-7P | 167007-21-8P | 167007-22-9P | 167007-23-0P | 167007-24-1P |
| 167007-25-2P | 167007-26-3P | 167007-27-4P | 167007-28-5P | 167007-29-6P |
| 167007-30-9P | 167007-31-0P | 167007-32-1P | 167007-33-2P | 167007-34-3P |
| 167007-35-4P | 167007-36-5P | 167007-37-6P | 167007-38-7P | 167007-39-8P |
| 167007-40-1P | 167007-41-2P | 167007-42-3P | 167007-43-4P | 167007-44-5P |
| 167007-45-6P | 167007-46-7P | 167007-47-8P | 167007-48-9P | 167007-49-0P |
| 167007-50-3P | 167007-51-4P | 167007-52-5P | 167007-53-6P | 167007-54-7P |
| 167007-55-8P | 167007-56-9P | 167007-57-0P | 167007-58-1P | 167007-59-2P |
| 167007-60-5P | 167007-61-6P | 167007-62-7P | 167007-63-8P | 167007-64-9P |
| 167007-65-0P | 167007-66-1P | | | |

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclyl biphenyls as **angiotensin II** antagonists)

L1 ANSWER 74 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
antagonists)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**angiotensin II**, antagonists, (biphenylylmethyl)tetrazole derivs.)

IT 167007-67-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and reaction of, in prepn. of **angiotensin II** antagonist)

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| 3775-61-9P | 124750-51-2P | 167004-85-5P | 167004-86-6P | 167004-87-7P |
| 167004-88-8P | 167004-89-9P | 167004-90-2P | 167004-91-3P | 167004-92-4P |
| 167004-93-5P | 167004-94-6P | 167004-95-7P | 167004-96-8P | 167004-97-9P |
| 167004-98-0P | 167004-99-1P | 167005-00-7P | 167005-01-8P | 167005-02-9P |
| 167005-03-0P | 167005-04-1P | 167005-05-2P | 167005-06-3P | 167005-07-4P |
| 167005-08-5P | 167005-09-6P | 167005-10-9P | 167005-11-0P | 167005-12-1P |
| 167005-13-2P | 167005-14-3P | 167005-15-4P | 167005-16-5P | 167005-17-6P |
| 167005-18-7P | 167005-19-8P | 167005-20-1P | 167005-21-2P | 167005-22-3P |
| 167005-23-4P | 167005-24-5P | 167005-25-6P | 167005-26-7P | 167005-27-8P |
| 167005-28-9P | 167005-29-0P | 167005-30-3P | 167005-31-4P | 167005-32-5P |
| 167005-33-6P | 167005-34-7P | 167005-35-8P | 167005-36-9P | 167005-37-0P |
| 167005-38-1P | 167005-39-2P | 167005-40-5P | 167005-41-6P | 167005-42-7P |
| 167005-43-8P | 167005-44-9P | 167005-45-0P | 167005-46-1P | 167005-47-2P |
| 167005-48-3P | 167005-49-4P | 167005-50-7P | 167005-51-8P | 167005-52-9P |
| 167005-53-0P | 167005-54-1P | 167005-55-2P | 167005-56-3P | 167005-57-4P |
| 167005-58-5P | 167005-59-6P | 167005-60-9P | 167005-61-0P | 167005-62-1P |
| 167005-63-2P | 167005-64-3P | 167005-65-4P | 167005-66-5P | 167005-67-6P |
| 167005-68-7P | 167005-69-8P | 167005-70-1P | 167005-71-2P | 167005-72-3P |
| 167005-73-4P | 167005-74-5P | 167005-75-6P | 167005-76-7P | 167005-77-8P |
| 167005-78-9P | 167005-79-0P | 167005-80-3P | 167005-81-4P | 167005-82-5P |
| 167005-83-6P | 167005-84-7P | 167005-85-8P | 167005-86-9P | 167005-87-0P |
| 167005-88-1P | 167005-89-2P | 167005-90-5P | 167005-91-6P | 167005-92-7P |
| 167005-93-8P | 167005-94-9P | 167005-95-0P | 167005-96-1P | 167005-97-2P |
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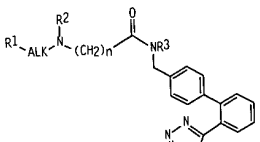
| 167006-31-7P | 167006-32-8P | 167006-33-9P | 167006-34-0P | 167006-35-1P |
| 167006-36-2P | 167006-37-3P | 167006-38-4P | 167006-39-5P | 167006-40-8P |
| 167006-41-9P | 167006-42-0P | 167006-43-1P | 167006-44-2P | 167006-45-3P |
| 167006-46-4P | 167006-47-5P | 167006-48-6P | 167006-49-7P | 167006-50-0P |
| 167006-51-1P | 167006-52-2P | 167006-53-3P | 167006-54-4P | 167006-55-5P |
| 167006-56-6P | 167006-57-7P | 167006-58-8P | 167006-59-9P | 167006-60-2P |

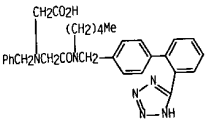
L1 ANSWER 75 OF 123 CAPLUS COPYRIGHT 2003 ACS

1995:742584 Document No. 123:144623 Preparation of alkylglycine derivatives with **angiotensin II** receptor antagonist activity. Sato, Atsushi; Nozawa, Yoshihisa (Taiho Pharmaceutical Co Ltd, Japan). Jpn. Kokai Tokkyo Koho JP 06287182 A2 19941011 Heisei, 27 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1994-11757 19940203. PRIORITY: JP 1993-18845 19930205.

GI



I



II

AB [[N-(N-alkylglycyl)aminomethyl]biphenylyl]tetrazole derivs. [I: R1 = (un)substituted Ph, naphthyl, heterocyclyl contg. 1 or 2 N, O, or S atoms; R2 = H, HO2CCH2, lower alkoxycarbonylmethyl; R3 = lower alkyl; R4 = H, trityl; ALK = lower alkylene; n = 0,1], also having antihypertensive activity and useful as cardiovascular agents for the treatment of hypertension, heart diseases, arteriosclerosis, and brain **cerebral apoplexy**, are prepd. Thus, 3.63 g N-n-pentyl-N-[[2'-(N-trityltetrazol-5-yl)biphenyl-4-yl]methyl]bromoacetamide (prepn. given) was dissolved in DMF followed by adding 1.50 g Et N-benzylglycinate and 600 mg NaHCO3 and the resulting mixt. was stirred at 100.degree. for 4 h to give, after detritylation with methanolic HCl and sapon. with 1 N aq. NaOH in MeOH, to give title compd. (II). A total of 51 I were prepd. and 14 I showed pA2, defined as -log(drug concn.) + log{[Ed50 (drug)/ED50 (control)] - 1}, of 8.49-10.03 for inhibiting the **angiotensin II**-induced contraction of rat thoreic aorta vs. 8.48 for the known **angiotensin II** receptor antagonist Dup-753.

TI Preparation of alkylglycine derivatives with **angiotensin II** receptor antagonist activity

AB . . . 0,1], also having antihypertensive activity and useful as

L1 ANSWER 75 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
cardiovascular agents for the treatment of hypertension, heart diseases, arteriosclerosis, and brain **cerebral apoplexy**, are prepd. Thus, 3.63 g N-n-pentyl-N-[[2'-(N-trityltetrazol-5-yl)biphenyl-4-yl]methyl]bromoacetamide (prepn. given) was dissolved in DMF followed by adding 1.50 g Et N-benzylglycinate and. . . and 14 I showed pA2, defined as -log(drug concn.) + log{[ED50 (drug)/ED50 (control)] - 1}, of 8.49-10.03 for inhibiting the **angiotensin II**-induced contraction of rat thoreic aorta vs. 8.48 for the known **angiotensin II** receptor antagonist Dup-753.

ST alkylglycine prepn **angiotensin II** receptor antagonist; antihypertensive alkylglycylaminomethylbiphenylyltetrazole; arteriosclerosis alkylglycylaminomethylbiphenylyltetrazole; brain **cerebral apoplexy** alkylglycylaminomethylbiphenylyltetraz ole; heart disease alkylglycylaminomethylbiphenylyltetrazole

IT Brain, disease
(**cerebral apoplexy**; prepn. of [[N-(N-alkylglycyl)aminomethyl]biphenylyl]tetrazole derivs. as **angiotensin II** receptor antagonists for treatment of heart disease and brain **cerebral apoplexy**)

IT Heart, disease
(prepn. of [[N-(N-alkylglycyl)aminomethyl]biphenylyl]tetrazole derivs. as **angiotensin II** receptor antagonists for treatment of heart disease and brain **cerebral apoplexy**)

IT Antiarteriosclerotics
Antihypertensives
(prepn. of [[N-(N-alkylglycyl)aminomethyl]biphenylyl]tetrazole derivs. as **angiotensin II** receptor antagonists, antihypertensives, and antiarteriosclerotics)

IT 6436-90-4P, Ethyl N-benzylglycinate 54608-35-4P, Ethyl N-(2-phenylethyl)glycinate 60857-16-1P, Ethyl N-p-methoxybenzylglycinate 79714-08-2P, Ethyl N-2-thienylmethylglycinate 81363-80-6P, Ethyl N-3-pyridylmethylglycinate 88720-42-7P, Ethyl N-o-chlorobenzylglycinate 88720-46-1P, Ethyl N-o-fluorobenzylglycinate 124750-51-2P 143096-13-3P 166592-13-8P 166592-45-6P 166592-46-7P 166592-47-8P 166592-48-9P 166592-49-0P 166592-50-3P 166592-51-4P 166592-52-5P 166592-53-6P 166592-54-7P, Ethyl N-m-chlorobenzylglycinate 166592-55-8P, Ethyl N-5-methyl-2-pyrazinylmethylglycinate 166592-56-9P, Ethyl N-benzyl-N-(tert-butoxylcarbonylmethyl)glycinate 166592-57-0P, Ethyl N-benzyl-N-(carboxymethyl)glycinate 166592-58-1P, Ethyl N-[2-(o-methylphenyl)ethyl]glycinate 166592-59-2P, Ethyl N-[2-(o-methoxyphenyl)ethyl]glycinate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate for prepn. of [[N-(N-alkylglycyl)aminomethyl]biphenylyl]t etrazole derivs. as **angiotensin II** receptor antagonists)

L1 ANSWER 75 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT 166591-98-6P 166591-99-7P 166592-00-3P 166592-01-4P 166592-02-5P 166592-03-6P 166592-04-7P 166592-05-8P 166592-06-9P 166592-07-0P 166592-08-1P 166592-09-2P 166592-10-5P 166592-11-6P 166592-12-7P 166592-13-8P 166592-14-9P 166592-15-0P 166592-16-1P 166592-17-2P 166592-18-3P 166592-19-4P 166592-20-7P 166592-21-8P 166592-22-9P 166592-23-0P 166592-24-1P 166592-25-2P 166592-26-3P 166592-27-4P 166592-28-5P 166592-29-6P 166592-30-9P 166592-31-0P 166592-32-1P 166592-33-2P 166592-34-3P 166592-35-4P 166592-36-5P 166592-37-6P 166592-38-7P 166592-39-8P 166592-40-1P 166592-41-2P 166592-42-3P 166592-43-4P 166592-44-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of [[N-(N-alkylglycyl)aminomethyl]biphenylyl]tetrazole derivs. as **angiotensin II** receptor antagonists)

IT 11128-99-7, **Angiotensin II**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(reaction in prepn. of [[N-(N-alkylglycyl)aminomethyl]biphenylyl]tetraz ole derivs. as **angiotensin II** receptor antagonists)

IT 64-04-0, 2-Phenylethylamine 100-46-9, Benzylamine, reactions 105-36-2, Ethyl bromoacetate 109-73-9, n-Butylamine, reactions 110-58-7, n-Pentylamine 5292-43-3, tert-Butyl bromoacetate 17846-68-3, Tributyltin azide 22118-09-8, Bromoacetyl chloride 114772-54-2, (2'-Cyanobiphenyl-4-ylmethyl)amine 124750-51-2, [2'-(N-Trityltetrazol-5-yl)biphenyl-4-yl]methyl bromide
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction in prepn. of [[N-(N-alkylglycyl)aminomethyl]biphenylyl]tetraz ole derivs. as **angiotensin II** receptor antagonists)

L1 ANSWER 76 OF 123 CAPLUS COPYRIGHT 2003 ACS
1995:533543 Document No. 122:287921 Role of **angiotensin II** in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rats. Wada, Takeo; Kanagawa, Rei; Ishimura, Yoshimasa; Inada, Yoshiyuki; Nishikawa, Kohei (Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., Osaka, 532, Japan). Journal of Hypertension, 13(1), 113-22 (English) 1995. CODEN: JOHYD3. ISSN: 0263-6352.

AB To study the effects of blockade of the renin-angiotensin system on the development of hypertension and end-organ damage in hyporeninemic deoxycorticosterone acetate (DOCA)-salt hypertensive rats, using an **angiotensin II** (Ang II) receptor antagonist (TCV-116) or an angiotensin converting enzyme (ACE) inhibitor (enalapril), DOCA-salt hypertensive rats were produced by uninephrectomy, implantation with DOCA pellets and 1% NaCl loading. TCV-116 (0.1 or 1 mg/kg) or enalapril (10 mg/kg) was given orally once a day from 3 to 6 wk after the operation. Body wt., blood pressure, plasma renin and creatinine, urinary protein and blood urea nitrogen were measured. After 3 wk treatment, edema and .omega.3-subtype benzodiazepine receptor binding in the brain were measured. Three weeks after the operation the blood pressure in the DOCA-salt hypertensive rats was approx. 200 mmHg, and the plasma renin concn. was lower than in sham-operated rats. However, after a further 3 wk the renin concn. was slightly above the normal level, and this increase was accompanied by a decrease in body wt. and increases in blood urea nitrogen, plasma creatinine, urinary protein and .omega.3-subtype benzodiazepine receptor binding in the cerebral cortex, and by brain edema. Treatment with TCV-116 or enalapril prevented renal damage and decrease in body wt. with little effect on blood pressure. Enalapril prevented brain edema and the increase in benzodiazepine binding in the brain cortex, and 1 mg/kg TCV-116 prevented them markedly. Although the hypertension in DOCA-salt hypertensive rats is independent of the renin-angiotensin system, the degree of cerebral and renal damage is assocd. with the activity of the renin-angiotensin system and has little relation with the blood pressure level.

TI Role of **angiotensin II** in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rats

AB . . . the renin-angiotensin system on the development of hypertension and end-organ damage in hyporeninemic deoxycorticosterone acetate (DOCA)-salt hypertensive rats, using an **angiotensin II** (Ang II) receptor antagonist (TCV-116) or an angiotensin converting enzyme (ACE) inhibitor (enalapril). DOCA-salt hypertensive rats were produced by uninephrectomy. . . .

ST angiotensin **cerebrovascular** kidney damage hypertension; deoxycorticosterone angiotensin damage hypertension

IT Brain, disease
Hypertension
(**angiotensin II** in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rat)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**angiotensin II**, **angiotensin II**

L1 ANSWER 76 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rat)

IT Kidney, disease
(injury, **angiotensin II** in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rat)

IT 64-85-7, Deoxycorticosterone
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**angiotensin II** in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rat)

IT 11128-99-7, **Angiotensin-II**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**angiotensin II** in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rat)

IT 9015-82-1, Dipeptidyl carboxypeptidase 9015-94-5, Renin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**angiotensin II** in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rat)

IT 75847-73-3, Enalapril 145040-37-5, TCV-116
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**angiotensin II** in **cerebrovascular** and renal damage in deoxycorticosterone acetate-salt hypertensive rat)

L1 ANSWER 77 OF 123 CAPLUS COPYRIGHT 2003 ACS
1995:215112 Document No. 122:1739 Angiotensin IV reverses the acute cerebral blood flow reduction after experimental **subarachnoid hemorrhage** in the rat. Naveri, Liisa; Stromberg, Christer; Saavedra, Juan M. (Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD, 20892, USA). Journal of Cerebral Blood Flow and Metabolism, 14(6), 1096-9 (English) 1994. CODEN: JCBMDN. ISSN: 0271-678X.

AB The effect of angiotensin (ANG) IV on CBF after exptl. **subarachnoid hemorrhage** (SAH) was studied in rats using laser-Doppler flowmetry. ANG IV (1 .mu.g/kg/min i.v.) or saline treatments were started 20 min after SAH. ANG IV increased CBF (from 45 to 84% of baseline) by 60 min. In the saline group, CBF remained low (51%). Pretreatment with the specific ANG II antagonist Sar1, Ile8-ANG II did not antagonize ANG IV. Detn. of nitric oxide synthase (NOS) activity in vitro or inhibition of NOS in vivo did not support a role for NO in the action of ANG IV.

TI Angiotensin IV reverses the acute cerebral blood flow reduction after experimental **subarachnoid hemorrhage** in the rat

AB The effect of angiotensin (ANG) IV on CBF after exptl. **subarachnoid hemorrhage** (SAH) was studied in rats using laser-Doppler flowmetry. ANG IV (1 .mu.g/kg/min i.v.) or saline treatments were started 20 min. . . .

ST angiotensin brain circulation **subarachnoid hemorrhage**

IT Brain
Circulation
(angiotensin degrdn. product reversal of cerebral blood flow redn. in **subarachnoid hemorrhage**)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**angiotensin II**, angiotensin degrdn. product reversal of cerebral blood flow redn. in **subarachnoid hemorrhage**)

IT Meninges
(diseases, **subarachnoid hemorrhage**, angiotensin degrdn. product reversal of cerebral blood flow redn. in **subarachnoid hemorrhage**)

IT 23025-68-5, Angiotensin IV
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiotensin degrdn. product reversal of cerebral blood flow redn. in **subarachnoid hemorrhage**)

IT 10102-43-9, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

L1 ANSWER 77 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
(angiotensin degrdn. product reversal of cerebral blood flow redn. in **subarachnoid hemorrhage** independent of nitric oxide)

IT 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(angiotensin degrdn. product reversal of cerebral blood flow redn. in **subarachnoid hemorrhage** independent of nitric oxide)

L1 ANSWER 78 OF 123 CAPLUS COPYRIGHT 2003 ACS
1994:646383 Document No. 121:246383 Endothelium-derived vasocontracting factor (EDCF): TXA2. Kurahashi, Kazuyoshi; Usui, Hachiro (Radioisot. Res. Cent., Kyoto Univ., Kyoto, 606, Japan). Igaku no Ayumi, 170(5), 416-19 (Japanese) 1994. CODEN: IGAYAY. ISSN: 0039-2359. Publisher: Ishiyaku Shuppan.

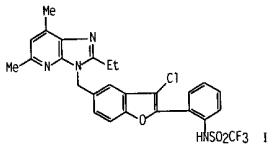
AB A review, with 12 refs., on the acetylcholine-dependent constriction of canine cerebral artery, which is endothelium-dependent contraction (EDC) sensitive to phospholipase A2 inhibitors, cyclooxygenase inhibitors, and TXA2 inhibitors. The EDC is not sensitive to lipoxygenase inhibitors. Serotonin-induced constriction is independent of endothelium. Noradrenaline, histamine, and **angiotensin II** induce EDC by release of TXA2 as does acetylcholine. Cerebrospinal fluid of **subarachnoid hemorrhage** induces EDC. The process of TXA2 release as endothelium-derived contracting factor (EDCF) is sensitive to nifedipine.

AB . . . and TXA2 inhibitors. The EDC is not sensitive to lipoxygenase inhibitors. Serotonin-induced constriction is independent of endothelium. Noradrenaline, histamine, and **angiotensin II** induce EDC by release of TXA2 as does acetylcholine. Cerebrospinal fluid of **subarachnoid hemorrhage** induces EDC. The process of TXA2 release as endothelium-derived contracting factor (EDCF) is sensitive to nifedipine.

IT 51-41-2, Noradrenaline 51-45-6, Histamine, biological studies 51-84-3, Acetylcholine, biological studies 11128-99-7, **Angiotensin II**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(endothelium-derived contracting factor TXA2 release in cerebral artery response to)

L1 ANSWER 79 OF 123 CAPLUS COPYRIGHT 2003 ACS
1994:579625 Document No. 121:179625 Antihypertensive [[[(Imidazopyridinyl)methyl]benzofuranyl]phenyl]methanesulfonamide Derivatives. Judd, Duncan Bruce (Glaxo Group Ltd., UK). PCT Int. Appl. WO 9411369 A1 19940526, 32 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1993-EP3157 19931111. PRIORITY: GB 1992-23860 19921113.

GI




I

AB Specific compds. were claimed, i.e. N-[2-[3-chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]phenyl]trifluoromethanesulfonamide (I); 3-[[3-chloro-2-[2-[[(trifluoromethyl)sulfonyl]amino]phenyl]-5-benzofuranyl]methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-MeOH; N-[2-[3-chloro-5-[[2-ethyl-5-[2-(hydroxypropyl)]-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulfonamide; 3-[[3-chloro-2-[2-[[(trifluoromethyl)sulfonyl]amino]phenyl]-5-benzofuranyl]methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-methano; N-[2-[3-chloro-5-[[5-[2-(hydroxypropyl)]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulfonamide. The invention further relates to processes for their prepn., pharmaceutical compns. contg. them, and to their use in medicine, particularly in the treatment of hypertension. The above compds. are claimed for the treatment fo congestive heart failure, renal insufficiency, renal failure, proteinuria, Bartter's syndrome, secondary hyperaldosteronism, Raynaud's syndrome, **cerebrovascular** insufficiency, peripheral vascular disease, diabetic retinopathy, glaucoma, cognitive disorders, CNS disorders, depression, schizophrenia, and anxiety.

AB . . . are claimed for the treatment fo congestive heart failure, renal insufficiency, renal failure, proteinuria, Bartter's syndrome, secondary hyperaldosteronism, Raynaud's syndrome, **cerebrovascular** insufficiency, peripheral vascular disease, diabetic retinopathy, glaucoma, cognitive disorders, CNS disorders, depression, schizophrenia, and anxiety.

IT Brain, disease
(**cerebrovascular** insufficiency, [[[(imidazopyridinyl)methyl]b

L1 ANSWER 79 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
enzofuranyl]phenyl]methanesulfonamides for treatment)
IT 11128-99-7, **Angiotensin II**
RL: RCT (Reactant); RACT (Reactant or reagent)
(antagonists. [[[(imidazopyridinyl)methyl]benzofuranyl]phenyl]methanesu
lfonamides)
IT 157725-81-0P 157725-82-1P 157725-83-2P 157725-84-3P 157725-85-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as **angiotensin II** antagonist)

L1 ANSWER 80 OF 123 CAPLUS COPYRIGHT 2003 ACS
1994:474532 Document No. 121:74532 **Angiotensin II** AT2
receptor stimulation increases **cerebrovascular** resistance during
hemorrhagic hypotension in rats. Naeveri, Liisa; Stroemberg, Christer;
Saavedra, Juan M. (Section on Pharmacology, Laboratory of Clinical
Science, National Institute of Mental Health, National Institutes of
Health, 9000 Rockville Pike, Bethesda, MD 20892, USA). Regulatory
Peptides, 52(1), 21-9 (English) 1994. CODEN: REPPDY. ISSN: 0167-0115.
AB The effects of the **angiotensin II** (ANG II) AT2 ligand
PD 123319 and the AT1 antagonist losartan on cerebral blood flow (CBF)
were studied during hemorrhagic hypotension in anesthetized rats using
laser-Doppler flowmetry. In the control group CBF remained stable when
mean arterial blood pressure (MABP) was lowered from 84 mmHg (baseline) to
45 mmHg, whereafter there was a pressure dependent decrease in CBF
indicating inadequacy of autoregulation. **Cerebrovascular**
resistance (CVR) was reduced until MABP 40 mmHg, where a max. dilation was
reached. PD 123319 dose-dependently (3-30 mg/kg i.v.) increased CVR
through all blood pressures. Losartan 3 mg/kg i.v. had an effect similar
to PD 123319. Selective stimulation of AT2 receptors with i.v. ANG II
infusion, in the presence of AT1 receptor blockade by losartan, also
increased CVR. As a result, reduced CBF was seen in the treatment groups.
The effects of ANG II and PD 123319 30 mg/kg were antagonized by the
nonselective ANG II antagonist Sar1,Ile8-ANG II (4 .mu.g/kg/min i.v.).
None of the treatments affected baseline CBF. The results confirm that
ANG II contributes to **cerebrovascular** resistance and
participates in the regulation of CBF apparently through AT2 receptors.
TI **Angiotensin II** AT2 receptor stimulation increases
**cerebrovascular** resistance during hemorrhagic hypotension in rats
AB The effects of the **angiotensin II** (ANG II) AT2 ligand
PD 123319 and the AT1 antagonist losartan on cerebral blood flow (CBF)
were studied during hemorrhagic. . . from 84 mmHg (baseline) to 45
mmHg, whereafter there was a pressure dependent decrease in CBF indicating
inadequacy of autoregulation. **Cerebrovascular** resistance (CVR)
was reduced until MABP 40 mmHg, where a max. dilation was reached. PD
123319 dose-dependently (3-30 mg/kg i.v.). . . Sar1,Ile8-ANG II (4
.mu.g/kg/min i.v.). None of the treatments affected baseline CBF. The
results confirm that ANG II contributes to **cerebrovascular**
resistance and participates in the regulation of CBF apparently through
AT2 receptors.
IT Brain
(circulation of, in hemorrhagic hypotension, **angiotensin**
**II** AT2 receptor regulation of)
IT Hemorrhage
(hypotension from, brain circulation in, **angiotensin**
**II** AT2 receptor regulation of)
IT Circulation
(of brain, in hemorrhagic hypotension, **angiotensin II**
AT2 receptor regulation of)

L1 ANSWER 80 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT Receptors
RL: BIOL (Biological study)
(**angiotensin II** AT2, in brain circulation
regulation, in hemorrhagic hypotension)
IT Hypotension
(hemorrhagic, brain circulation in, **angiotensin II**
AT2 receptor regulation of)
IT 4474-91-3, Human **angiotensin II** 114798-26-4,
Losartan 130663-39-7, PD 123319
RL: BIOL (Biological study)
(brain circulation in response to, in hemorrhagic hypotension)

L1 ANSWER 81 OF 123 CAPLUS COPYRIGHT 2003 ACS
1994:450765 Document No. 121:50765 The role of **angiotensin**
**II** in the regulation of **cerebrovascular** function in the
rat. Saavedra, Juan M. (Laboratory of Clinical Science, National
Institute of Mental Health, Bethesda, MD, 20892, USA). Pharmaceutical and
Pharmacological Letters, 3(6), 256-9 (English) 1994. CODEN: PPLEE3.
ISSN: 0939-9488.
AB **Angiotensin II** has been proposed to play a role in
**cerebrovascular** control. With quant. autoradiog. and selective
competitors, the authors demonstrated **angiotensin II**
AT2 receptors in rat cerebral arteries. Selective **angiotensin**
**II** AT1 and AT2 receptor ligands modulate the upper limit of the
cerebral blood flow autoregulation. **Angiotensin II**
AT2 receptor stimulation with an **angiotensin II**
infusion in the presence of the AT1 antagonist losartan extends the upper
limit of cerebral blood flow autoregulation. Similar results were
obtained with the AT2 selective ligands PD 123319 and CGP 42112, and with
administration of losartan alone. These results indicate a significant
role for the **angiotensin II** system in the regulation
of **cerebrovascular** tone. Selective nonpeptidic AT1 and AT2
compds. could be useful for the treatment or prevention of
**cerebrovascular** disorders.
TI The role of **angiotensin II** in the regulation of
**cerebrovascular** function in the rat
AB **Angiotensin II** has been proposed to play a role in
**cerebrovascular** control. With quant. autoradiog. and selective
competitors, the authors demonstrated **angiotensin II**
AT2 receptors in rat cerebral arteries. Selective **angiotensin**
**II** AT1 and AT2 receptor ligands modulate the upper limit of the
cerebral blood flow autoregulation. **Angiotensin II**
AT2 receptor stimulation with an **angiotensin II**
infusion in the presence of the AT1 antagonist losartan extends the upper
limit of cerebral blood flow autoregulation. Similar results. . .
ligands PD 123319 and CGP 42112, and with administration of losartan
alone. These results indicate a significant role for the
**angiotensin II** system in the regulation of
**cerebrovascular** tone. Selective nonpeptidic AT1 and AT2 compds.
could be useful for the treatment or prevention of **cerebrovascular**
disorders.
ST brain circulation **angiotensin II**
IT Brain
(circulation of, **angiotensin II** regulation of)
IT Circulation
(of brain, **angiotensin II** regulation of)
IT Receptors
RL: BIOL (Biological study)
(**angiotensin II** AT1, in brain circulation
regulation)
IT Receptors
RL: BIOL (Biological study)
(**angiotensin II** AT2, in brain circulation
regulation)

L1 ANSWER 81 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT Artery, composition
(cerebral, **angiotensin II** AT2 receptor of)
IT 4474-91-3, Human **angiotensin II**
RL: BIOL (Biological study)
(brain circulation in response to)
IT 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(receptor for, in brain circulation regulation)

L1 ANSWER 82 OF 123 CAPLUS COPYRIGHT 2003 ACS
1994:260880 Document No. 120:260880 Quinapril prevents stroke both during and after the treatment period in stroke-prone spontaneously hypertensive rats. Vacher, Elisabeth; Fornes, Paul; Domergue, Valerie; Richer, Christine; Bruneval, Patrick; Giudicelli, Jean Francois (Dep. Pharmacol., Fac. Med., Paris-Sud, Fr.). American Journal of Hypertension, 6(11, Pt. 1), 951-9 (English) 1993. CODEN: AJHYE6. ISSN: 0895-7061.
AB The effects of long-term oral administration of quinapril on the occurrence of stroke and on mortality were investigated in young, salt-loaded, stroke-prone spontaneously hypertensive rats (SHR-SPs) during the treatment period (8th-34th week of age) and for .ltoreq.6 wk thereafter. Simultaneously, blood pressure, salt intake, diuresis, and proteinuria were investigated at regular intervals, and **cerebrovascular**, renal, and cardiac lesions were assessed after death. Quinapril completely suppressed stroke and mortality, afforded only limited protection against the blood pressure rise, and prevented increases in salt intake, diuresis, and proteinuria both during and after the treatment period. Quinapril long-lastingly prevented vascular fibrinoid necrosis development at the cerebral, but also at the renal and cardiac, levels. In the kidneys, vascular intimal and medial hyperplasias were strongly reduced, as were the glomerular and tubulointerstitial lesions. At the cardiac level, intimal and medial hyperplasias were slightly reduced but infarction and fibrosis were hardly affected. As the renin-angiotensin system is highly stimulated in SHR-SPs and as **angiotensin II (AII)** is responsible for fibrinoid necrosis formation, vessel obstruction, and stroke in these animals, it is concluded that the long-lasting protection afforded by quinapril against stroke and mortality in SHR-SPs both during and after the treatment period is mostly due to the drug-induced interruption of the renin-angiotensin system. The resulting suppression of **AII** also prevents renal and, to a lesser extent, cardiac damage.
AB . . . age) and for .ltoreq.6 wk thereafter. Simultaneously, blood pressure, salt intake, diuresis, and proteinuria were investigated at regular intervals, and **cerebrovascular**, renal, and cardiac lesions were assessed after death. Quinapril completely suppressed stroke and mortality, afforded only limited protection against the. . . slightly reduced but infarction and fibrosis were hardly affected. As the renin-angiotensin system is highly stimulated in SHR-SPs and as **angiotensin II (AII)** is responsible for fibrinoid necrosis formation, vessel obstruction, and stroke in these animals, it is concluded that the long-lasting protection. . . and after the treatment period is mostly due to the drug-induced interruption of the renin-angiotensin system. The resulting suppression of **AII** also prevents renal and, to a lesser extent, cardiac damage.

L1 ANSWER 83 OF 123 CAPLUS COPYRIGHT 2003 ACS
1994:213748 Document No. 120:213748 **Cerebrovascular** autoregulation in response to hypertension induced by NG-nitro-L-arginine methyl ester. Kelly, P. A. T.; Thomas, C. L.; Ritchie, I. M.; Arbuthnott, G. W. (Dep. Clin. Neurosci., Univ. Edinburgh, Edinburgh, UK). Neuroscience (Oxford, United Kingdom), 59(1), 13-20 (English) 1994. CODEN: NRSCDN. ISSN: 0306-4522.
AB Local neocortical blood flow and glucose utilization were measured in conscious rats using [14C]iodoantipyrine and [14C]2-deoxyglucose quant. autoradiog., resp., following i.v. injection of the nitric oxide synthase inhibitor NG-nitro-L-arginine Me ester (L-NAME) (30 mg/kg). The dose of L-NAME was chosen to produce a level of hypertension equiv. to that produced in a parallel group of rats by the infusion of **angiotensin-II** (5 .mu.g/mL at 0.5-2.0 mL/h). In those animals in which angiotensin-induced hypertension did not exceed 150 mmHg (mean arterial blood pressure), there were no significant effects upon cortical blood flow when compared to controls, but at higher pressures (157 mmHg), blood flow was significantly increased in circumscribed areas of cortex, most notably in parietal (from 204 to 780 mL/100 g/ min) and occipital cortex (from 175 to 600 mL/100 g per min), while other cortical areas (e.g. temporal and frontal areas) were unchanged. Despite the fact that L-NAME Me ester increased blood pressure to levels (164 mmHg) which were in excess of the highest produced by angiotensin, there was no evidence of focal hyperemia; indeed blood flow was significantly reduced in every cortical region except parietal area 1. No significant differences in glucose use were evident between any of the groups. Apparently, by influencing **cerebrovascular** tone, nitric oxide may play a role in detg. the upper limit of autoregulation, but also inhibition of nitric oxide synthesis may result in a dissocn. of blood flow from the metabolic demands of cortical tissues.
TI **Cerebrovascular** autoregulation in response to hypertension induced by NG-nitro-L-arginine methyl ester
AB . . . to produce a level of hypertension equiv. to that produced in a parallel group of rats by the infusion of **angiotensin-II** (5 .mu.g/mL at 0.5-2.0 mL/h). In those animals in which angiotensin-induced hypertension did not exceed 150 mmHg (mean arterial blood. . . except parietal area 1. No significant differences in glucose use were evident between any of the groups. Apparently, by influencing **cerebrovascular** tone, nitric oxide may play a role in detg. the upper limit of autoregulation, but also inhibition of nitric oxide. . .
IT Hypertension
(**cerebrovascular** autoregulation response to, nitric oxide role in)
IT 10102-43-9, Nitric oxide, biological studies
RL: BIOL (Biological study)
(**cerebrovascular** autoregulation mediated by)
IT 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(hypertension induced by, **cerebrovascular** autoregulation response to, nitric oxide in relation to)
IT 50-99-7, D-Glucose, biological studies

L1 ANSWER 83 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: BIOL (Biological study)
(uptake of, by brain, **cerebrovascular** autoregulation and nitric oxide in relation to)

L1 ANSWER 84 OF 123 CAPLUS COPYRIGHT 2003 ACS
1994:127189 Document No. 120:127189 Chronic lead exposure in rats: effects on blood pressure. Nowack, R.; Wiecek, A.; Exner, B.; Gretz, N.; Ritz, E. (Dep. Intern. Med., Univ. Heidelberg, Heidelberg, Germany). European Journal of Clinical Investigation, 23(7), 433-43 (English) 1993. CODEN: EJCIB8. ISSN: 0014-2972.
AB The influence of Pb exposure on blood pressure was investigated in Wistar Kyoto, Sprague Dawley and stroke prone spontaneously hypertensive rats. In short-term expts., a dose-dependent decrease of blood pressure was found with administration of Pb acetate in drinking fluid. This effect was more pronounced in young, male as compared to old, female animals. Pressor responses to noradrenaline and ANG II were decreased. In contrast, long-term Pb exposure of more than 1 yr duration consistently caused hypertension. In SHR-sp a high proportion of animals died from **cerebrovascular** hemorrhage even before developing hypertension. Chronically Pb exposed hypertensive rats had increased plasma vol. and total body sodium despite normal renal function. Plasma concns. of catecholamines and PRA were normal. The results show a biphasic effect of Pb on blood pressure. An important role of renal sodium retention in chronic Pb-induced exptl. hypertension is suggested.
AB . . . Pb exposure of more than 1 yr duration consistently caused hypertension. In SHR-sp a high proportion of animals died from **cerebrovascular** hemorrhage even before developing hypertension. Chronically Pb exposed hypertensive rats had increased plasma vol. and total body sodium despite normal. . .
IT 51-41-2, Noradrenaline 7440-09-7, Potassium, biological studies 7440-23-5, Sodium, biological studies 7440-70-2, Calcium, biological studies 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(lead effect on blood pressure in relation to)

L1 ANSWER 85 OF 123 CAPLUS COPYRIGHT 2003 ACS
1993:573911 Document No. 119:173911 Effect of chronic treatment with losartan on development of hypertension in stroke-prone spontaneously hypertensive rats (SHRSP): comparative study with enalapril and hydralazine. Okada, Megumu; Kobayashi, Masahiko; Satoh, Noriko; Nishikibe, Masaru; Ikemoto, Fumihiko (Tsukuba Res. Inst., Banyu Pharm. Co., LTD., Tsukuba, Japan). Hypertension Research, 16(1), 49-55 (English) 1993. CODEN: HRESE4. ISSN: 0916-9636.
AB SHRSP were treated with the title drugs at 5 to 13 wk of age. The **angiotensin II** antagonist losartan (10 mg/kg/day), enalapril (3 mg/kg/day) and hydralazine (30 mg/kg/day) inhibited the age-related development of hypertension; in addn., blood pressure in the losartan and enalapril groups, but not in the hydralazine group, remained lower than that in controls for .ltoreq.15 wk after discontinuation of treatment. Heart wt. in the losartan and enalapril groups was lower than that in controls at the ages of 16 and 29 wk, while there was no difference in heart wt. with hydralazine. At the age of 29 wk, **cerebrovascular** lesions, as judged by the histochem. obsd. leakage of parenterally infused horseradish peroxidase from the vessels, were decreased in all drug-treated groups, but the effect was most prominent in the group treated with losartan. Plasma renin activity and immunoreactive renin content in the juxtaglomerular cells were lower than those in controls. Losartan at 1 mg/kg/day had no appreciable effect on blood pressure, heart wt., plasma renin and angiotensin-converting enzyme activities, or immunoreactive renin content in the juxtaglomerular cells. These results suggest that the blockade of **angiotensin II** yields a persistent antihypertensive effect accompanied by protection of cerebral vessels from lesions and of the heart from hypertrophy.
AB SHRSP were treated with the title drugs at 5 to 13 wk of age. The **angiotensin II** antagonist losartan (10 mg/kg/day), enalapril (3 mg/kg/day) and hydralazine (30 mg/kg/day) inhibited the age-related development of hypertension; in addn., blood. . . 16 and 29 wk, while there was no difference in heart wt. with hydralazine. At the age of 29 wk, **cerebrovascular** lesions, as judged by the histochem. obsd. leakage of parenterally infused horseradish peroxidase from the vessels, were decreased in all. . . renin and angiotensin-converting enzyme activities, or immunoreactive renin content in the juxtaglomerular cells. These results suggest that the blockade of **angiotensin II** yields a persistent antihypertensive effect accompanied by protection of cerebral vessels from lesions and of the heart from hypertrophy.
IT 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(-renin system in spontaneous hypertension, losartan and enalapril and hydralazine effect on)

L1 ANSWER 86 OF 123 CAPLUS COPYRIGHT 2003 ACS
1993:462704 Document No. 119:62704 Stroke prevention by losartan in stroke-prone spontaneously hypertensive rats. Stier, Charles T., Jr.; Adler, Lawrence A.; Levine, Seymour; Chander, Praveen N. (Dep. Pharmacol., New York Med. Coll., Valhalla, NY, 10595, USA). Journal of Hypertension, 11(3), S37-S42 (English) 1993. CODEN: JOHYD3. ISSN: 0263-6352.
AB Treatment with the **angiotensin II** antagonist losartan at 30 mg/kg/day, orally, delayed the development of severe hypertension and prevented stroke in saline-drinking stroke-prone spontaneously hypertensive rats (SHRSP); doses of 10 mg/kg/day did not affect the hypertension but prevented the occurrence of **cerebrovascular** lesions until age .gtoreq.28 wk. These and other data are consistent with the theory that **angiotensin II** has an effect on the pathophysiol. of **cerebrovascular** lesion development in saline-drinking SHRSP and that losartan protects against such development in the absence of a blood pressure fall.
AB Treatment with the **angiotensin II** antagonist losartan at 30 mg/kg/day, orally, delayed the development of severe hypertension and prevented stroke in saline-drinking stroke-prone spontaneously hypertensive rats (SHRSP); doses of 10 mg/kg/day did not affect the hypertension but prevented the occurrence of **cerebrovascular** lesions until age .gtoreq.28 wk. These and other data are consistent with the theory that **angiotensin II** has an effect on the pathophysiol. of **cerebrovascular** lesion development in saline-drinking SHRSP and that losartan protects against such development in the absence of a blood pressure fall.
IT Brain, disease
(stroke, losartan inhibition of, in stroke-prone hypertension, **angiotensin II** in relation to)
IT Hypertension
(stroke-prone spontaneous, losartan inhibition of, **angiotensin II** in relation to)
IT 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(stroke-prone spontaneous hypertension inhibition by losartan in relation to)
IT 114798-26-4, Losartan
RL: BIOL (Biological study)
(stroke-prone spontaneous hypertension inhibition by, **angiotensin II** in relation to)

L1 ANSWER 87 OF 123 CAPLUS COPYRIGHT 2003 ACS
1993:440818 Document No. 119:40818 Acute cocaine alters **cerebrovascular** autoregulation in the rat neocortex. Kelly, Paul A. T.; Sharkey, John; Philip, Ross; Ritchie, Isobel M. (Dep. Clin. Neurosci., Univ. Edinburgh, Edinburgh, EH4 2XU, UK). Brain Research Bulletin, 31(5), 581-5 (English) 1993. CODEN: BRBUDU. ISSN: 0361-9230.
AB Although cocaine abuse has been assocd. with an increased incidence of **cerebrovascular** accident, the underlying mechanisms are unknown. In this study, the authors have investigated the effects of cocaine upon the autoregulation of local cortical blood flow (ICBF) during hypertension. Hypertension was induced in conscious rats by i.v. infusion of **angiotensin-II** (5 .mu.g/mL; 0.5-2.5 mL/h), and animals were subsequently injected IV with either cocaine-HCl (5 mg/kg) or saline, prior to the measurement of ICBF or glucose utilization (ICGU) using [14C]-iodoantipyrine or [14C]-2-deoxyglucose quant. autoradiog., resp. Hypertension alone (<155 mmHg) did not significantly alter ICBF in any cortical areas examd. However, at higher mean arterial blood pressure (MABP), ICBF increased focally (+265%) in parietal cortex. Cocaine did not alter ICBF in normotensive animals, but with increasing levels of hypertension (MABP > 145 mmHg), all cocaine-treated rats showed focal increases (200-400%) in ICBF in parietal cortex. Glucose use remained relatively unaffected in all treatment groups. This hyperemia in cocaine-treated rats at MABP below the normal upper limit of autoregulation may provide a mechanism to explain hemorrhagic stroke in cocaine abusers.
TI Acute cocaine alters **cerebrovascular** autoregulation in the rat neocortex
AB Although cocaine abuse has been assocd. with an increased incidence of **cerebrovascular** accident, the underlying mechanisms are unknown. In this study, the authors have investigated the effects of cocaine upon the autoregulation of local cortical blood flow (ICBF) during hypertension. Hypertension was induced in conscious rats by i.v. infusion of **angiotensin-II** (5 .mu.g/mL; 0.5-2.5 mL/h), and animals were subsequently injected IV with either cocaine-HCl (5 mg/kg) or saline, prior to the. . .
ST cocaine **cerebrovascular** autoregulation hypertension
IT 50-36-2, Cocaine
RL: BIOL (Biological study)
(brain circulation autoregulation response to, in hypertension, **cerebrovascular** accidents in relation to)

L1 ANSWER 88 OF 123 CAPLUS COPYRIGHT 2003 ACS
1993:400553 Document No. 119:553 Control of blood pressure and end-organ damage in maturing salt-loaded stroke-prone spontaneously hypertensive rats by oral **angiotensin II** receptor blockade.
Camargo, Maria Jose F.; Von Lutterotti, Nicola; Campbell, Wallace G., Jr.; Pecker, Mark S.; James, Gary D.; Timmermans, Pieter B.; Laragh, John H. (Med. Coll., Cornell Univ., New York, NY, 10021, USA). Journal of Hypertension, 11(1), 31-40 (English) 1993. CODEN: JOHYD3. ISSN: 0263-6352.

AB The authors aimed to study the effects of renin-angiotensin system blockade by a novel non-peptide **angiotensin II** receptor antagonist, losartan, on development of hypertension and acceleration of end-organ damage in salt-loaded stroke-prone spontaneously hypertensive rats (SHRSP). One hundred and eighty-one male SHRSP were fed a 4% sodium diet from 6 to 18 wk of age. Seventy-eight SHRSP were treated orally with losartan, 30 mg/kg per day. One hundred and three rats constituted untreated controls. Blood pressure, plasma renin activity (PRA), renal function and end-organ damage were monitored during the transition to malignant hypertension. Losartan prevented a blood pressure rise during the first 4 wk of salt loading. Thereafter, blood pressure rose slowly in losartan-treated rats; however, at each time-point studied blood pressure was significantly lower in losartan-treated rats than in control rats. Losartan treatment increased PRA during the first 4 wk, but this effect was not sustained. Thereafter, PRA decreased to control (week 0) levels. In contrast, 2 wk after high-sodium feeding started, untreated SHRSP failed to suppress PRA appropriately; thereafter, PRA rose significantly. Losartan affected renal pathophysiol. by blunting the decline in glomerular filtration rate, controlling proteinuria and preventing or delaying the appearance of malignant nephrosclerosis. Losartan treatment significantly increased survival and completely prevented **cerebrovascular** infarcts. The results indicate that **angiotensin II** blockade markedly reduces both hypertension and end-organ damage in chronically salt-loaded SHRSP and that the renin-angiotensin system may play an important role in the development of hypertensive cardiovascular disease in SHRSP.

TI Control of blood pressure and end-organ damage in maturing salt-loaded stroke-prone spontaneously hypertensive rats by oral **angiotensin II** receptor blockade

AB The authors aimed to study the effects of renin-angiotensin system blockade by a novel non-peptide **angiotensin II** receptor antagonist, losartan, on development of hypertension and acceleration of end-organ damage in salt-loaded stroke-prone spontaneously hypertensive rats (SHRSP). One. . . rate, controlling proteinuria and preventing or delaying the appearance of malignant nephrosclerosis. Losartan treatment significantly increased survival and completely prevented **cerebrovascular** infarcts. The results indicate that **angiotensin II** blockade markedly reduces both hypertension and end-organ damage in chronically salt-loaded SHRSP and

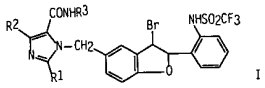
L1 ANSWER 88 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
that the renin-angiotensin system may play an. . .

IT Antihypertensives
(**angiotensin II** antagonist as, in stroke-prone spontaneous hypertension)

IT Kidney, disease
(injury, in salt-loaded stroke-prone spontaneous hypertension, **angiotensin II** antagonist block of)

L1 ANSWER 89 OF 123 CAPLUS COPYRIGHT 2003 ACS
1993:169107 Document No. 118:169107 Preparation of antihypertensive benzofuran derivatives with N-linked 1H-imidazolylmethyl-5-carboxamide substituents. Ross, Barry Clive; Middlemiss, David; Scopes, David Ian Carter; Jack, Torquil Iain MacLean; Cardwell, Kevin Stuart; Dowle, Michael Dennis; Judd, Duncan Bruce (Glaxo Group Ltd., UK). Eur. Pat. Appl. EP 514216 A1 19921119, 27 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1992-304448 19920515. PRIORITY: GB 1991-10635 19910516.

GI



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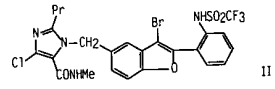

II

AB Title compds. I (R1 = Et, Pr; R2 = Cl, Me, Et; R3 = H, Me, Et), were prepd. Thus, 1,1-dimethylethyl [2-(3-bromo-5-methyl-2-benzofuranyl)phenyl]carbamate (prepn. from 5-methylbenzofuran given) was converted in several steps to title compd. II. In a test for antihypertensive activity in renal-ligated hypertensive rats, II at 0.5 mg/kg orally showed a diastolic blood pressure redn. after 7 h of 60 (no units given). I are **angiotensin II** antagonists and are useful in treatment of cognitive disorders (no data). Pharmaceutical formulations contg. I are given.

AB . . . at 0.5 mg/kg orally showed a diastolic blood pressure redn. after 7 h of 60 (no units given). I are **angiotensin II** antagonists and are useful in treatment of cognitive disorders (no data). Pharmaceutical formulations contg. I are given.

IT Brain, disease
(**cerebrovascular** insufficiency, treatment of, benzofuranylimidazolecarboxamides for)

IT 11128-99-7, **Angiotensin II**
RL: RCT (Reactant); RACT (Reactant or reagent)
(anti)

L1 ANSWER 90 OF 123 CAPLUS COPYRIGHT 2003 ACS
1993:144836 Document No. 118:144836 Alterations of cerebromicrovascular Na+,K+-ATPase activity due to fatty acids and acute hypertension.
Caspers, Mary Lou; Bussone, Mary; Dow, Matthew J.; Ulanski II, Lawrence J.; Grammas, Paula (Dep. Chem., Univ. Detroit Mercy, Detroit, MI, USA). Brain Research, 602(2), 215-20 (English) 1993. CODEN: BRREAP. ISSN: 0006-8993.

AB Acute hypertension, induced in rats by i.v. injection of **angiotensin II**, previously has been shown to increase **cerebrovascular** permeability to macromols. The purpose of this study was to examine the effect of acute hypertension on Na+,K+-ATPase, the enzyme responsible for controlling ionic permeability of the cerebromicrovascular endothelium. The K+-dependent p-nitrophenylphosphatase activity of the cerebromicrovascular Na+,K+-ATPase was detd. using microvessels prepd. from hypertensive and normotensive rats. When compared to controls, a 70% decrease in the max. rate (Vmax) of the Na+,K+-ATPase from hypertensive rats was evident with no change in the Michaelis const. (KM). In contrast, .gamma.-glutamyltranspeptidase, a marker enzyme for cerebral endothelial cells, was not affected. Sodium arachidonate (1-100 .mu.M) inhibited the phosphatase activity of the Na+,K+-ATPase in microvessels isolated from both normotensive and hypertensive rats in a dose-dependent manner. Furthermore, poly-unsatd. fatty acids (sodium linoleate and arachidonate) evoked the greatest inhibition of the enzyme, while sodium oleate and sodium palmitate inhibited the Na+,K+-ATPase to lesser extents. This regulation of enzyme activity by fatty acids was comparable in control and hypertensive groups. In summary, the data indicate that the cerebromicrovascular Na+,K+-ATPase was altered as a consequence of acute hypertension and that poly-unsatd. fatty acids can modulate this enzyme in microvessels from either hypertensive or control rats.

AB Acute hypertension, induced in rats by i.v. injection of **angiotensin II**, previously has been shown to increase **cerebrovascular** permeability to macromols. The purpose of this study was to examine the effect of acute hypertension on Na+,K+-ATPase, the enzyme. . .

L1 ANSWER 91 OF 123 CAPLUS COPYRIGHT 2003 ACS
1992:646043 Document No. 117:246043 **Angiotensin II** receptor antagonist delays renal damage and stroke in salt-loaded Dahl salt-sensitive rats. Von Lutterotti, Nicola; Camargo, Maria J. F.; Campbell, Wallace G., Jr.; Mueller, Franco B.; Timmermans, Pieter B.; Sealey, Jean E.; Laragh, John H. (Med. Coll., Cornell Univ., New York, NY, 10021, USA). Journal of Hypertension, 10(9), 949-57 (English) 1992. CODEN: JOHYD3. ISSN: 0263-6352.

AB The effects of blockade of the renin-angiotensin system upon the development of hypertension, end-organ damage, and mortality in Dahl salt-sensitive (DSS) rats were studied using an **angiotensin II** receptor antagonist, losartan. Losartan blunted the Na-induced blood pressure rise only transiently. Salt loading suppressed plasma renin activity (PRA) in both groups until week 4 and thereafter it rose more markedly in the treated group. With no treatment, renal lesions were first detected at 2 wk and strokes at 6 wk. However, losartan transiently decreased the incidence and delayed the progression of renal damage and **cerebrovascular** lesions (strokes) and increased survival. PRA correlated with renal damage and the incidence of strokes in both groups. Blood pressure only partially affected survival, but did not correlate with stroke incidence. Thus, although the rise in blood pressure is dependent upon Na loading, morbidity and mortality in salt-loaded DSS rats are assocd. with activation of the renin-angiotensin system and are only partially related to blood pressure.

TI **Angiotensin II** receptor antagonist delays renal damage and stroke in salt-loaded Dahl salt-sensitive rats

AB . . . renin-angiotensin system upon the development of hypertension, end-organ damage, and mortality in Dahl salt-sensitive (DSS) rats were studied using an **angiotensin II** receptor antagonist, losartan. Losartan blunted the Na-induced blood pressure rise only transiently. Salt loading suppressed plasma renin activity (PRA) in. . . wk and strokes at 6 wk. However, losartan transiently decreased the incidence and delayed the progression of renal damage and **cerebrovascular** lesions (strokes) and increased survival. PRA correlated with renal damage and the incidence of strokes in both groups. Blood pressure. . .

IT Receptors
RL: BIOL (Biological study)
(**angiotensin II**, kidney damage and stroke response to sodium loading in relation to)

IT 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(receptors for, kidney damage and stroke response to sodium loading mediation by)

L1 ANSWER 92 OF 123 CAPLUS COPYRIGHT 2003 ACS
1992:585511 Document No. 117:185511 Angiotensin AT2 receptors regulate cerebral blood flow in rats. Stomberg, Christer; Naveri, Liisa; Saavedra, Juan M. (Lab. Clin. Sci., Natl. Inst. Ment. Health, Bethesda, MD, 20892, USA). NeuroReport, 3(8), 703-4 (English) 1992. CODEN: NERPEZ. ISSN: 0959-4965.

AB Large cerebral arteries have been reported to contain angiotensin receptors that are exclusively of the AT2 subtype. The effect of the AT2 receptor selective ligand PD 123319 on cerebral blood flow (CBF) in rats was measured by using a laser-doppler flowmeter. PD 123319 (1-10 mg/kg) dose-dependently inhibited the increase in CBF, when the blood pressure was increased by a norepinephrine infusion. However, PD 123319 did not alter baseline CBF at normal blood pressures. Therefore PD 123319 appears to interfere with the autoregulatory mechanisms of CBF. The participation of AT2 receptors in the regulation of CBF confirms a physiol. role for this receptor subtype, and may give clues for future treatment of various **cerebrovascular** disorders.

AB . . . regulation of CBF confirms a physiol. role for this receptor subtype, and may give clues for future treatment of various **cerebrovascular** disorders.

IT Receptors
RL: BIOL (Biological study)
(**angiotensin II** AT2, cerebral blood flow regulation by)

L1 ANSWER 93 OF 123 CAPLUS COPYRIGHT 2003 ACS
1992:253443 Document No. 116:253443 Clinical studies on serum apolipoproteins in **cerebrovascular** diseases. Tsugu, Yasukuni (Med. Sch., Nagoya City Univ., Nagoya, 467, Japan). Nagoya-shiritsu Daigaku Igakkai Zasshi, 42(4), 877-90 (Japanese) 1991. CODEN: NASDA6. ISSN: 0027-7606.

AB **Cerebral infarction** (CI) patients <59 yr old showed different blood apolipoprotein levels depending on artery disease. CI patients >60 yr old showed no specific tendency. The blood levels of apolipoproteins in controls were 135.0, 31.4, 97.5, 4.49, 8.87, and 4.50 mg/dL for AI, **AII**, B, CII, CIII, and E, resp.. CI patients with the distribution of a perforating artery (CIPA) exhibited increased levels of 14.9, 6.30, 13.28, and 6.19 mg/dL for B, CII, CIII and E, resp., in the acute phase. CI patients with a distribution of a cortical artery (CICA) showed lower blood levels for AI and **AII** as 115.4 and 27.3 mg/dL, resp. in acute phase. The level of AI in encephalorrhagia was decreased slightly at 122.9 mg/dL. CICA in chronic phase >1 mo after onset of the disease remained unchanged. CIPA in chronic phase showed increased blood levels of B, CIII, and E at 114.3, 11.33, and 5.76 mg/dL, resp. Encephalorrhagia in the chronic phase showed lower AI and **AII** levels as 122.5 and 27.5 mg/dL, resp. Acute phase CICA with diabetes mellitus (DM) showed higher levels of CII at 10.43 mg/dL. Acute phase CIPA with DM showed higher CIII levels of 13.79 mg/dL than CIPA without DM. Blood apolipoprotein levels in CICA were not different between primary and recurrent diseases. Recurrent CIPA showed lower blood levels of AI, **AII**, CII, and CIII. CIPA without recurrence showed high CII and CIII levels. The AI level appears to be an atherogenicity index, whereas CII reflects repair of infarction.

TI Clinical studies on serum apolipoproteins in **cerebrovascular** diseases

AB **Cerebral infarction** (CI) patients <59 yr old showed different blood apolipoprotein levels depending on artery disease. CI patients >60 yr old showed. . . specific tendency. The blood levels of apolipoproteins in controls were 135.0, 31.4, 97.5, 4.49, 8.87, and 4.50 mg/dL for AI, **AII**, B, CII, CIII, and E, resp.. CI patients with the distribution of a perforating artery (CIPA) exhibited increased levels of. . . the acute phase. CI patients with a distribution of a cortical artery (CICA) showed lower blood levels for AI and **AII** as 115.4 and 27.3 mg/dL, resp. in acute phase. The level of AI in encephalorrhagia was decreased slightly at 122.9. . . B, CIII, and E at 114.3, 11.33, and 5.76 mg/dL, resp. Encephalorrhagia in the chronic phase showed lower AI and **AII** levels as 122.5 and 27.5 mg/dL, resp. Acute phase CICA with diabetes mellitus (DM) showed higher levels of CII at. . . apolipoprotein levels in CICA were not different between primary and recurrent diseases. Recurrent CIPA showed lower blood levels of AI, **AII**, CII, and CIII. CIPA without recurrence showed high CII and CIII levels. The AI level appears to be an atherogenicity. . .

ST blood apolipoprotein **cerebrovascular** disease diabetes

IT Diabetes mellitus
(apolipoproteins of blood serum of humans with **cerebrovascular** diseases and)

IT Lipoproteins

L1 ANSWER 93 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: BIOL (Biological study)
(apo-, A-I, of blood serum of humans with **cerebrovascular** diseases and diabetes)

IT Lipoproteins
RL: BIOL (Biological study)
(apo-, A-II, of blood serum of humans with **cerebrovascular** diseases and diabetes)

IT Lipoproteins
RL: BIOL (Biological study)
(apo-, B, of blood serum of humans with **cerebrovascular** diseases and diabetes)

IT Lipoproteins
RL: BIOL (Biological study)
(apo-, C-II, of blood serum of humans with **cerebrovascular** diseases and diabetes)

IT Lipoproteins
RL: BIOL (Biological study)
(apo-, C-III, of blood serum of humans with **cerebrovascular** diseases and diabetes)

IT Lipoproteins
RL: BIOL (Biological study)
(apo-, E, of blood serum of humans with **cerebrovascular** diseases and diabetes)

IT Brain, disease
(**cerebrovascular**, apolipoproteins of blood serum of humans with)

L1 ANSWER 94 OF 123 CAPLUS COPYRIGHT 2003 ACS
1992:212340 Document No. 116:212340 Apolipoprotein levels in preeclamptic pregnancies. Kobayashi, Shinichi; Tanaka, Masanobu; Masaki, Kazuo; Hirakawa, Shun; Momose, Kazuo (Sch. Med., Toho Univ., Tokyo, Japan). Nippon Sanka Fujinka Gakkai Zasshi, 44(2), 223-8 (Japanese) 1992. CODEN: NISFAY. ISSN: 0300-9165.

AB Lipoprotein is known to increase during pregnancy but the factors responsible for the change have not been established. In addn., the lipoprotein concn. in preeclamptic pregnancy is higher than in normal pregnancy. The apolipoproteins are an important determinant of metab. and the structure of plasma lipoproteins. In normal pregnancies, nonpregnancies and preeclamptic pregnancies the levels of blood apolipoproteins AI, **AII**, B and E were detd. by **TIA** methods. In normal pregnancies, the concns. of apolipoproteins AI, **AII**, B and E were 182.6 mg/dL (n = 12), 33.3 mg/dL, 128.6 mg/dL, and 6.8 mg/dL, resp. In the nonpregnancies, the concns. of apolipoproteins AI, **AII**, B and E were 135.6 mg/dL (n = 5), 30.8 mg/dL, 76.0 mg/dL, and 4.4 mg/dL, resp. In the preeclamptic pregnancy, the concns. of apolipoproteins AI, **AII**, B and E were 181.0 mg/dL (n = 22), 33.2 mg/dL, 145.7 mg/dL and 5.8 mg/dL, resp. The concn. of apolipoprotein B in preeclamptic pregnancy was higher and apolipoprotein E was lower than in normal pregnancies. Thus, the measurement of apolipoprotein is useful for the evaluation of preeclamptic pregnancy.

AB . . . metab. and the structure of plasma lipoproteins. In normal pregnancies, nonpregnancies and preeclamptic pregnancies the levels of blood apolipoproteins AI, **AII**, B and E were detd. by **TIA** methods. In normal pregnancies, the concns. of apolipoproteins AI, **AII**, B and E were 182.6 mg/dL (n = 12), 33.3 mg/dL, 128.6 mg/dL, and 6.8 mg/dL, resp. In the nonpregnancies, the concns. of apolipoproteins AI, **AII**, B and E were 135.6 mg/dL (n = 5), 30.8 mg/dL, 76.0 mg/dL, and 4.4 mg/dL, resp. In the preeclamptic pregnancy, the concns. of apolipoproteins AI, **AII**, B and E were 181.0 mg/dL (n = 22), 33.2 mg/dL, 145.7 mg/dL and 5.8 mg/dL, resp. The concn. of. . .

L1 ANSWER 95 OF 123 CAPLUS COPYRIGHT 2003 ACS
1992:166025 Document No. 116:166025 The lipoxygenase inhibitor phenidone protects against proteinuria and stroke in stroke-prone spontaneously hypertensive rats. Munsiff, Amar V.; Chander, Praveen N.; Levine, Seymour; Stier, Charles T., Jr. (Dep. Pharmacol., New York Med. Coll., Valhalla, NY, 10595, USA). American Journal of Hypertension, 5(2), 56-63 (English) 1992. CODEN: AJHYE6. ISSN: 0895-7061.

AB The present study examd. whether the dual cyclooxygenase/lipoxygenase inhibitor phenidone would protect stroke-prone spontaneously hypertensive rats (SHRSP) from stroke and hypertensive renal disease. Vehicle-treated SHRSP fed stroke-prone rodent diet and 1% saline, exhibited severe systolic blood pressure elevation (261 mmHg), marked proteinuria (90 mg/day), and stroke, with an av. age at death of 14 wk. In a second group of six saline-loaded SHRSP, treatment with phenidone (60 mg/kg/day) was started at 8.4 wk of age. Despite establishment of severe hypertension in this group (274 mmHg), proteinuria remained at basal levels (28 mg/day), and signs of stroke were absent through at least 16 wk of age. Phenidone treatment also prevented the declines in body wt. and food intake obsd. in vehicle-treated SHRSP, and maintained urine vol. and saline intake. Serum 12-hydroxyeicosatetraenoic acid (12-HETE) generation was significantly inhibited >50% in incubates of whole blood from phenidone-treated SHRSP. It has been previously shown that agents which interfere with the renin-angiotensin system afford protection from renal and **cerebrovascular** injury in saline-loaded SHRSP; cyclooxygenase inhibition alone will hasten the onset of these pathol. changes. Whether phenidone, which has been reported to attenuate **angiotensin II**-mediated effects, affords vascular protection by interference with lipoxygenase-mediated action of **angiotensin II** remains to be elucidated.

AB . . . phenidone-treated SHRSP. It has been previously shown that agents which interfere with the renin-angiotensin system afford protection from renal and **cerebrovascular** injury in saline-loaded SHRSP; cyclooxygenase inhibition alone will hasten the onset of these pathol. changes. Whether phenidone, which has been reported to attenuate **angiotensin II**-mediated effects, affords vascular protection by interference with lipoxygenase-mediated action of **angiotensin II** remains to be elucidated.

L1 ANSWER 96 OF 123 CAPLUS COPYRIGHT 2003 ACS
1992:99181 Document No. 116:99181 Effects of halothane in low concentrations on cerebral blood flow, cerebral metabolism, and **cerebrovascular** autoregulation in the baboon. Bruessel, Thomas; Fitch, William; Brodner, Gerhard; Arendt, Irena; Van Aken, Hugo (Klin. Poliklin. Anaesthesiol. Oper. Intensivmed., Westfael. Wilhelms-Univ., Muenster, 4400, Germany). Anesthesia & Analgesia (Baltimore, MD, United States), 73(6), 758-64 (English) 1991. CODEN: AACRAT. ISSN: 0003-2999.

AB Halothane in anesthetic concns. caused cerebral vasodilatation and decreases cerebral oxygen consumption (CMRO). The purpose of this study was to evaluate cerebral blood flow (CF) and (CMRO) changes assocd. with low concns. of halothane. In 8 normoventilated baboons with background anesthesia maintained with phencyclidine and nitrous oxide, CBF and CMRO were studied during the administration of end-tidal concns. of halothane (0.12,3 0.25, 0.375, 0.5, 0.75, and 1.0 vol.%). Arterial blood pressure was supported by an infusion of **angiotensin II** amide at 0.75 and 1.0 vol.% of halothane to maintain an adequate cerebral perfusion pressure. In addn., **cerebrovascular** autoregulation was tested before and during the administration of 0.375, 0.75, and 1.0 vol.% of halothane. **Cerebrovascular** autoregulation was assessed by observing the response of CBF to an acute increase in mean arterial pressure produced by angiotensin. CMRO decreased as the concn. of halothane was increased. At low halothane concns. (0.125-0.375 vol.%), CBF decreased; however, at concns. above 0.375 vol.%, CBF increased with a decrease in **cerebrovascular** resistance. Autoregulation was intact during 0.375 vol.% of halothane, but with 0.75 and 1.0 vol.% of halothane, CBF was passively dependent on cerebral perfusion pressure, suggesting impaired autoregulation.

TI Effects of halothane in low concentrations on cerebral blood flow, cerebral metabolism, and **cerebrovascular** autoregulation in the baboon

AB . . . concns. of halothane (0.12,3 0.25, 0.375, 0.5, 0.75, and 1.0 vol.%). Arterial blood pressure was supported by an infusion of **angiotensin II** amide at 0.75 and 1.0 vol.% of halothane to maintain an adequate cerebral perfusion pressure. In addn., **cerebrovascular** autoregulation was tested before and during the administration of 0.375, 0.75, and 1.0 vol.% of halothane. **Cerebrovascular** autoregulation was assessed by observing the response of CBF to an acute increase in mean arterial pressure produced by angiotensin. . . . At low halothane concns. (0.125-0.375 vol.%), CBF decreased; however, at concns. above 0.375 vol.%, CBF increased with a decrease in **cerebrovascular** resistance. Autoregulation was intact during 0.375 vol.% of halothane, but with 0.75 and 1.0 vol.% of halothane, CBF was passively. . .

ST halothane brain circulation oxygen; **cerebrovascular** autoregulation halothane

IT Anesthetics
(halothane, cerebral circulation and metab. and **cerebrovascular** autoregulation response to low concns. of)

IT Brain, disease
(**cerebrovascular**, halothane-induced, autoregulation impairment in relation to)

L1 ANSWER 96 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT Circulation
(systemic, halothane effect on, **cerebrovascular** autoregulation in relation to)

IT 151-67-7, Halothane
RL: BIOL (Biological study)
(cerebral circulation and metab. and **cerebrovascular** autoregulation response to low concns. of)

L1 ANSWER 97 OF 123 CAPLUS COPYRIGHT 2003 ACS
1992:35134 Document No. 116:35134 Endothelin-1 and big endothelin cause **subarachnoid hemorrhage** in the anesthetized rabbit.
Huneidi, A. Hamid S.; Thiemermann, Christoph; Lidbury, Paul S.; D'Orleans-Juste, Pedro; Anggard, Erik E.; Afshar, Farhad; Vane, John R. (Med. Coll., St. Bartholomew's Hosp., London, EC1M 6BQ, UK). Journal of Cardiovascular Pharmacology, 17(Suppl. 7), S492-S495 (English) 1991. CODEN: JCPCDT. ISSN: 0160-2446.

AB Intra-arterial injection of endothelin-1 (ET-1) (1 nmol/kg) or human big endothelin-1 (b-ET-1; 3 nmol/kg) into anesthetized rabbits produced a rise in left ventricular systolic pressure (LVSP) and caused **subarachnoid hemorrhage** (SAH) in 75 and 88% of the expts., resp. In all animals, the SAH occurred in the subarachnoid space around the distal part of the basilar artery complex. The cyclooxygenase inhibitor indomethacin (5 mg/kg i.v.) potentiated the pressor effect of both peptides, and all animals pretreated with indomethacin prior to ET-1 or b-ET developed SAH. In contrast, rabbits treated with vehicle (saline), indomethacin alone, or the carboxy-terminal fragment of b-ET (CT 22-38; 3 nmol/kg i.a.) developed neither a rise in LVSP nor SAH. A rise in blood pressure alone is unlikely to account for the SAH brought about by the peptides for **angiotensin II** (1 nmol/kg/min for 30 min) produced a greater increment in LVSP than ET-1 or b-ET, but did not cause SAH. In addn., there was no correlation between the rise in LVSP produced by ET-1 or b-ET and the severity of the SAH.

TI Endothelin-1 and big endothelin cause **subarachnoid hemorrhage** in the anesthetized rabbit

AB . . . human big endothelin-1 (b-ET-1; 3 nmol/kg) into anesthetized rabbits produced a rise in left ventricular systolic pressure (LVSP) and caused **subarachnoid hemorrhage** (SAH) in 75 and 88% of the expts., resp. In all animals, the SAH occurred in the subarachnoid space around. . . SAH. A rise in blood pressure alone is unlikely to account for the SAH brought about by the peptides for **angiotensin II** (1 nmol/kg/min for 30 min) produced a greater increment in LVSP than ET-1 or b-ET, but did not cause SAH.. . .

ST endothelin **subarachnoid hemorrhage**

IT Prostaglandins
RL: BIOL (Biological study)
(**subarachnoid hemorrhage** induction by endothelin-1 and big endothelin modulation by)

IT Meninges
(diseases, **subarachnoid hemorrhage**, endothelin-1 and big endothelin induction of)

IT Blood pressure
(systolic, **subarachnoid hemorrhage** induction by endothelin-1 and big endothelin independent of)

IT 120796-97-6, Endothelin-38 (human) 123626-67-5, Endothelin-1
RL: BIOL (Biological study)
(**subarachnoid hemorrhage** induction by)

L1 ANSWER 98 OF 123 CAPLUS COPYRIGHT 2003 ACS
1992:15600 Document No. 116:15600 **Cerebrovascular** effects of angiotensin converting enzyme inhibition involve large artery dilatation in rats. Postiglione, Alfredo; Bobkiewicz, Teresa; Vinholdt-Pedersen, Erik; Lassen, Niels A.; Paulson, Olaf B.; Barry, David I. (Neurobiol. Res. Group, Rigshosp., Den.). Stroke, 22(11), 1363-8 (English) 1991. CODEN: SJCCA7. ISSN: 0039-2499.

AB The aim of the study was to selectively examine the effects of converting enzyme inhibition on the large brain arteries by using concomitant inhibition of carbonic anhydrase to cause severe dilatation of mainly parenchymal resistance vessels. Cerebral blood flow was measured using the xenon-133 injection technique in three groups of Wistar rats either during carbonic anhydrase inhibition with acetazolamide (treatment A), during carbonic anhydrase inhibition followed by converting enzyme inhibition with captopril 40 min later (treatment B), or during carbonic anhydrase inhibition preceded by converting enzyme inhibition 20 min earlier (treatment C). After treatment A, cerebral blood flow rose rapidly and stabilized within 20 min at an av. of 220 mL/100 g/min; flow remained stable until at least 60 min. After treatment B, cerebral flow increased by a further 17.4%, from an av. of 219 mL/100 g/min to an av. of 257 mL/100 g/min. After treatment C, cerebral blood flow stabilized at an av. of 238 mL/100 g/min, with flow from 20 to 60 min always being higher (from 5% to 17%) than during carbonic anhydrase inhibition alone. Thus the addnl. inhibition of converting enzyme resulted in higher cerebral blood flow than during inhibition of carbonic anhydrase along. These results suggest that converting enzyme inhibition reduced resistance of large brain arteries and support the hypothesis that there is some **angiotensin II**-induced tone in large cerebral arteries.

TI **Cerebrovascular** effects of angiotensin converting enzyme inhibition involve large artery dilatation in rats

AB . . . results suggest that converting enzyme inhibition reduced resistance of large brain arteries and support the hypothesis that there is some **angiotensin II**-induced tone in large cerebral arteries.

ST ACE inhibition **cerebrovascular** system artery dilation; angiotensin converting enzyme inhibition brain circulation; vasodilation brain circulation ACE inhibition

IT 59-66-5
RL: BIOL (Biological study)
(**cerebrovascular** effects of angiotensin converting enzyme inhibition after carbonic anhydrase inhibition by, large artery dilation in)

IT 62571-86-2, Captopril
RL: BIOL (Biological study)
(**cerebrovascular** effects of angiotensin converting enzyme inhibition by, large artery dilation in)

IT 9015-82-1, Angiotensin converting enzyme
RL: BIOL (Biological study)
(inhibitors of, **cerebrovascular** effects of, large artery dilation in)

L1 ANSWER 97 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

L1 ANSWER 99 OF 123 CAPLUS COPYRIGHT 2003 ACS
1991:624184 Document No. 115:224184 Characterization of AT2 **angiotensin II** receptors in rat anterior cerebral arteries. Tsutsumi, Keisuke; Saavedra, Juan M. (Lab. Clin. Sci., Natl. Inst. Ment. Health, Bethesda, MD, 20892, USA). American Journal of Physiology, 261(3, Pt. 2), H667-H670 (English) 1991. CODEN: AJPHAP. ISSN: 0002-9513.

AB Quant. autoradiog. using the agonist 125I-Sar1-antiotensin II was used to localize and characterize **angiotensin II** (AT) receptors in the anterior cerebral artery of the male rat. This artery showed a moderately high no. of AT receptors, localized throughout the arterial wall. The no. of receptors was higher (125 fmol/mg protein) in arteries from young 2-wk-old rats compared with those in adult 8-wk-old rats (43 fmol/mg protein). In the anterior cerebral artery, AT binding was insensitive to displacement with the selective AT1 antagonist DuP 753 but was readily displaced by the selective AT2 antagonist CGP-42112 A nicotinic acid-Tyr-(N.SIGMA.-benzyloxycarbonyl-Arg)Lys-His-Pro-Ile-OH) (a concn. eliciting 50% of max. inhibition: 6 .times. 10-1-M). This indicated that the AT receptors in the cerebral artery were of the AT2 subtype. AT may exert its effects on cerebral circulation by stimulation of AT2 receptors, and these receptors may play a role during **cerebrovascular** development.

TI Characterization of AT2 **angiotensin II** receptors in rat anterior cerebral arteries

AB Quant. autoradiog. using the agonist 125I-Sar1-antiotensin II was used to localize and characterize **angiotensin II** (AT) receptors in the anterior cerebral artery of the male rat. This artery showed a moderately high no. of AT. . . may exert its effects on cerebral circulation by stimulation of AT2 receptors, and these receptors may play a role during **cerebrovascular** development.

IT Development, mammalian
(**angiotensin II** receptor of cerebral artery in)

IT Receptors
RL: BIOL (Biological study)
(for **angiotensin II**, AT2, of cerebral artery, characterization of)

IT Artery, composition
(cerebral, anterior, **angiotensin II** receptor of, characterization of)

IT 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(receptor for, of cerebral artery, characterization of)

L1 ANSWER 100 OF 123 CAPLUS COPYRIGHT 2003 ACS
1991:490241 Document No. 115:90241 Alterations of monoamine metabolites and neurotransmitters in cerebrospinal fluid of patients after **subarachnoid hemorrhage**. Sato, Kazuei (Neurol. Inst., Tokyo Women's Med. Coll., Tokyo, 162, Japan). Tokyo Joshi Ika Daigaku Zasshi, 61(5), 381-91 (Japanese) 1991. CODEN: TJIZAF. ISSN: 0040-9022.
AB Sequential changes in adrenaline (AD), noradrenaline (NA), dopamine (DA), serotonin (5HT) and their metabolites DOPAC, MHPG, HVA, 5-HIAA and other neuropeptides, GABA, somatostatin-like immunoreactivity (SS), TRH, arginine vasopressin (AV), angiotensin I and II in CSF were confirmed by high performance liq. chromatog. (HPLC) or RIA (RIA) or radio receptor assay (RRA) in 24 patients with **subarachnoid hemorrhage** (SAH) after aneurysmal rupture. Cerebrospinal fluid (CSF) samples were collected from patients with SAH 3 times during the course, in the acute stage (0-3 days after SAH), in the subacute stage (4-19 days), and in the chronic stage (after 20 days). Sequential changes in metabolites, neurol. status, and neuroradiog. findings of patients were evaluated. Changes in CSF levels of substances differed variously after SAH. For example, CSF levels of AD, NA, MHPG, GABA, SS, VP, and AG II were high and those of HVA, 5-HIAA and TRH were low in the acute stage, and gradually converged to the normal range with time. NA, GABA, SS, TRH, and VP were produced mainly in the hypothalamus, and different changes of these substances were considered to be the result of differential activation of brainstem-hypothalamic axis after SAH. A relationship was noted between changes in CSF levels and neurol. status, but not between CSF levels of substances and vol. of clot in subarachnoid space. CSF MHPG levels of the "Spasm" group were significantly higher than the "No spasm" group after 4th day after ictus and CSF NA levels did not differ between the 2 groups, but NA metab. (MHPG/NA ratio) in the "Spasm" group was higher than that of the "No spasm" group from 4 to 19 days after SAH. Increased activation of NA-MHPG metabolic pathway was therefore considered in the "Spasm" group from 4 to 19 days after SAH.
TI Alterations of monoamine metabolites and neurotransmitters in cerebrospinal fluid of patients after **subarachnoid hemorrhage**
AB . . . were confirmed by high performance liq. chromatog. (HPLC) or RIA (RIA) or radio receptor assay (RRA) in 24 patients with **subarachnoid hemorrhage** (SAH) after aneurysmal rupture. Cerebrospinal fluid (CSF) samples were collected from patients with SAH 3 times during the course, in. . .
ST cerebrospinal fluid monoamine metabolite **subarachnoid hemorrhage**; neurotransmitter cerebrospinal fluid **subarachnoid hemorrhage**
IT Cerebrospinal fluid
(monoamine metabolites and neurotransmitters in, after **subarachnoid hemorrhage**, in humans)
IT Meninges
(diseases, **subarachnoid hemorrhage**, monoamine

L1 ANSWER 100 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
metabolites and neurotransmitters in cerebrospinal fluid after, in humans)
IT 50-67-9, Serotonin, biological studies 51-41-2, Noradrenaline 51-43-4, Adrenaline 51-61-6, Dopamine, biological studies 54-16-0, 5-Hydroxyindole-3-acetic acid, biological studies 56-12-2, .gamma.-Aminobutyric acid, biological studies 102-32-9, 3, 4-Dihydroxyphenyl acetic acid 113-79-1, Arginine-vasopressin 306-08-1, Homovanillic acid 534-82-7 9041-90-1, Angiotensin I 11128-99-7, **Angiotensin II** 24305-27-9, TRH 51110-01-1, Somatostatin
RL: BIOL (Biological study)
(in cerebrospinal fluid, after **subarachnoid hemorrhage**, in humans)

L1 ANSWER 101 OF 123 CAPLUS COPYRIGHT 2003 ACS
1991:400667 Document No. 115:667 The influence of a cryogenic brain injury on the **cerebrovascular** response to isoflurane in the rabbit. Ramani, R.; Todd, Michael M.; Warner, David S. (Coll. Med., Univ. Iowa, Iowa City, IA, USA). Journal of Cerebral Blood Flow and Metabolism, 11(3), 388-97 (English) 1991. CODEN: JCBMDN. ISSN: 0271-678X.
AB To det. if an acute neurol. injury alters the **cerebrovascular** response to isoflurane, rabbits were anesthetized with morphine/N2O and mech. ventilated. Group 1 animals served as controls and received no injury. In Groups 2 and 3 a 30-s cryogenic injury was produced in the left parietal region using liq. N2 poured into a funnel affixed to the surface of the skull. Regional cerebral blood flow (CBF) was measured using microspheres. In Groups 2 and 3, flow was detd. before and 30 and 90 min after injury. After the 90-min data were collected, 1% (.apprxeq.1.0 MAC) isoflurane was administered to uninjured rabbits in Groups 1 and to lesioned rabbits in Group 3. A mean arterial pressure of .gtoreq.80 mm Hg was maintained during isoflurane administration by an infusion of **angiotensin II**. In Group 1, 2% isoflurane produced bilaterally sym. increases in hemispheric CBF, from 76 to 150 mL/100 g. CBF in the hindbrain increased from 91 to 248 mL/100 g.cntdot.min. Group 3, 2% isoflurane changed CBF in the lesioned hemisphere from 56 to only 77 mL/100 g.cntdot.min, while in the contralateral hemisphere, CBF rose from 68 to 97 mL/100 g.cntdot.min. Thus, a cryogenic injury attenuates the normal CBF response to a volatile anesthetic, both in the damaged hemisphere as well as in apparently uninjured regions distant from the injury focus. A similar cryogenic injury abolished the CBF response to changing PaCO2 in the injured hemisphere, but not in the contralateral hemisphere or the cerebellum. The CBF effects of isoflurane may be mediated via intermediary neurogenic and/or biochem. process.
TI The influence of a cryogenic brain injury on the **cerebrovascular** response to isoflurane in the rabbit
AB To det. if an acute neurol. injury alters the **cerebrovascular** response to isoflurane, rabbits were anesthetized with morphine/N2O and mech. ventilated. Group 1 animals served as controls and received no. . . in Group 3. A mean arterial pressure of .gtoreq.80 mm Hg was maintained during isoflurane administration by an infusion of **angiotensin II**. In Group 1, 2% isoflurane produced bilaterally sym. increases in hemispheric CBF, from 76 to 150 mL/100 g. CBF in. . .

L1 ANSWER 102 OF 123 CAPLUS COPYRIGHT 2003 ACS
1990:565426 Document No. 113:165426 Aza-2-bicyclooctane[2.2.2]carboxylic acids, and pharmaceutical compositions containing them, for treatment of arteritis and disorders of the microcirculation and of the vascular wall. Teisseire, Bernard (ADIR et Cie., Fr.). Fr. Demande FR 2635684 A1 19900302, 14 pp. (French). CODEN: FRXXBL. APPLICATION: FR 1988-11157 19880824.
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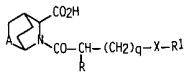


I

AB The title compds. I [A = vinylene or dimethylene; q = 0, 1; R = lower alkyl capable of carrying amino; X = S and R1 = H; or X = NH and R1 H or CH(COR2)R3 (R2 = OH, lower alkoxy; R3 = H, linear or branched alkyl, cycloalkyl, or phenylalkyl, etc.)] are provided for treatment of arteritis, esp. of the lower limbs, as well as for treatment of disorders in cerebral circulation, diabetic retinopathy, migraine, etc. Thus, normal and ischemic (ligatured) cremaster muscle prepns. were either untreated or treated with I. There was no difference in red-cell velocity or vessel diam. in normal untreated or treated prepns.; in prepns. with induced ischemia the mean diam. of the arterioles was improved in treated animals in comparison to controls, and red-cell velocity was normalized by treatment for 21 days. Among treated animals, red-cell velocity and blood flow measured 7 days after ligature did not show significant differences from values obtained for nonischemic prepns. A compressed tablet formulation (1000 tablets) contained (S) [(S)-ethoxycarbonyl-1-phenyl-3-propylamino)-2-oxo-1-propyl]-2-carboxy-3-(S)-azo-2-bicyclo[2.2.2]octane 300 mg, hydroxypropylcellulose 2, wheat starch 10, lactose 100, Mg stearate 3, and talc 3 g.
IT Senescence
(disorder, **cerebrovascular**, azabicyclooctane carboxylic acids for treatment of)
IT 9041-90-1, Angiotensin I 11002-13-4, Angiotensinogen (protein renin substrate) 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(artery contraction induction by, azabicyclooctane carboxylic acids for microcirculation disorder treatment effect on)

L1 ANSWER 103 OF 123 CAPLUS COPYRIGHT 2003 ACS

1990:421600 Document No. 113:21600 Relation of plasma renin to end organ damage and to protection of potassium feeding in stroke-prone hypertensive rats. Volpe, Massimo; Camargo, Maria J. F.; Mueller, Franco B.; Campbell, Wallace G., Jr.; Sealey, Jean E.; Pecker, Mark S.; Sosa, R. Ernest; Laragh, John H. (Cardiovasc. Cent., CUMC, New York, NY, 10021, USA). Hypertension, 15(3), 318-26 (English) 1990. CODEN: HPRTDN. ISSN: 0194-911X.

AB The effects were studied of regular diet (0.35% NaCl/1.1% potassium), high sodium diet (4% NaCl/0.75% potassium), or high sodium and high potassium diet (4% NaCl/2.11% potassium) on blood pressure, plasma renin activity, renal and **cerebrovascular** lesions, and incidence of stroke and mortality in male stroke-prone spontaneously hypertensive rats (SHRSP). In the first 4 wk, the rise in blood pressure was higher in high NaCl than in high NaCl/high potassium or regular diet groups. By 8 and 12 wk, the blood pressure in all 3 groups was similar. After 4 wk of diet, plasma renin activity was similar in the three groups and were not related to sodium excretion. After 8 wk, plasma renin activity was increased only in the high NaCl group, and by 12 wk plasma renin activity was higher in the high NaCl group than in the high NaCl/high potassium or in the regular diet groups. Moderate to severe renal vascular lesions were first detected in the high NaCl group by 8 wk of diet. At 12 wk, renal vascular damage index was higher in the high NaCl group than in the high NaCl/high potassium and regular diet groups. Incidence of stroke was 81% in high NaCl, 24.5% in high NaCl/high potassium, and 7.7% in regular diet groups. The increase in mortality, stroke, and renal and **cerebrovascular** lesions in SHRSP fed a high sodium diet is assocd. with a paradoxical rise in plasma renin activity. The protective effect of high potassium in SHRSP fed a high potassium diet is related to a lower blood pressure at 2-4 wk and a lower plasma renin activity, but not a lower blood pressure at 8-12 wk. This rise in plasma renin activity demonstrates that a high potassium diet suppresses or delays a primary or secondary paradoxical rise in plasma renin activity and thus, **angiotensin II** in the rats fed a high sodium diet. This action together with possible direct effects of potassium in the vasculature contributes to the protective effect on end organ damage and stroke in SHRSP.

AB . . . NaCl/0.75% potassium), or high sodium and high potassium diet (4% NaCl/2.11% potassium) on blood pressure, plasma renin activity, renal and **cerebrovascular** lesions, and incidence of stroke and mortality in male stroke-prone spontaneously hypertensive rats (SHRSP). In the first 4 wk, the. . . NaCl, 24.5% in high NaCl/high potassium, and 7.7% in regular diet groups. The increase in mortality, stroke, and renal and **cerebrovascular** lesions in SHRSP fed a high sodium diet is assocd. with a paradoxical rise in plasma renin activity. The protective. . . that a high potassium diet suppresses or delays a primary or secondary paradoxical rise in plasma renin activity and thus, **angiotensin** II in the rats fed a high sodium diet. This action together with possible direct effects of potassium in the vasculature. . .

L1 ANSWER 104 OF 123 CAPLUS COPYRIGHT 2003 ACS

1990:211856 Document No. 112:211856 Fulminant hypertension in transgenic rats harboring the mouse Ren-2 gene. Mullins, J. J.; Peters, J.; Ganten, D. (Dep. Pharmacol., Univ. Heidelberg, Heidelberg, D-6900, Germany). Nature (London, United Kingdom), 344(6266), 541-4 (English) 1990. CODEN: NATUAS. ISSN: 0028-0836.

AB Primary hypertension is a polygenic condition in which blood pressure is enigmatically elevated; it remains a leading cause of cardiovascular disease and death due to **cerebral hemorrhage**, cardiac failure, and kidney disease. The genes for several of the proteins involved in blood pressure homeostasis were cloned and characterized, including those of the renin-angiotensin system, which plays a central part in blood pressure control. The mouse Ren-2 renin gene was introduced into the genome of the rat and expression of this gene caused severe hypertension. These transgenic animals represent a model for hypertension in which the genetic basis for the disease is known. Further, as the transgenic animals do not overexpress active renin in the kidney and have low levels of active renin in their plasma, they also provide a new model for low-renin hypertension.

AB . . . condition in which blood pressure is enigmatically elevated; it remains a leading cause of cardiovascular disease and death due to **cerebral hemorrhage**, cardiac failure, and kidney disease. The genes for several of the proteins involved in blood pressure homeostasis were cloned and. . .

IT 9041-90-1, Angiotensin I 11128-99-7, **Angiotensin II**
RL: PRP (Properties)
(in transgenic fulminant hypertensive rats)

L1 ANSWER 103 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

L1 ANSWER 105 OF 123 CAPLUS COPYRIGHT 2003 ACS

1990:91660 Document No. 112:91660 The cerebral pressure - flow relationship during 1.0 MAC isoflurane anesthesia in the rabbit: the effect of different vasopressors. Patel, P. M.; Mutch, W. A. C. (Fac. Med., Univ. Manitoba, Winnipeg, MB, Can.). Anesthesiology, 72(1), 118-24 (English) 1990. CODEN: ANESAV. ISSN: 0003-3022.

AB The effects of different vasopressors on the cerebral pressure-flow relationship during 1.0 MAC isoflurane anesthesia were studied. Mean arterial pressure (MAP) was increased by one of 3 vasopressors [**angiotensin II** (AT), norepinephrine (NE), or phenylephrine (PE)] in 3 groups of New Zealand white rabbits. Regional cerebral blood flow (CBF) was measured at 5 intervals by the injection of radioactive microspheres at a stable 2.05% (1.0 MAC) end-tidal isoflurane concn. (baseline) and following elevation of MAP by 20, 40, 60, and 80% above baseline MAP with either AT, NE, or PE. Baseline MAP was the same in all groups. No differences in MAP were seen between groups when MAP was elevated from 20 to 80% above baseline. Normocapnia (PaCO2 35.8-38.2 mmHg) was maintained throughout. Total CBF (tCBF), hemispheric CBF (hCBF), and posterior fossa (cerebellum and brain stem) CBF (pCBF) were detd. Baseline tCBF, hCBF, and pCBF were similar in all groups. For all regions examd., the slope of the pressure-flow curve was less steep when MAP was elevated with AT vs. NE or PE. There was no difference in slope between the NE and PE groups for any region. Thus, either NE and PE may indirectly result in cerebral vasodilation or AT has intrinsic cerebral vasoconstrictive effects during 1.0 MAC isoflurane anesthesia in the rabbit. The choice of vasopressor critically influences the interpretation of whether **cerebrovascular** autoregulation is intact during isoflurane anesthesia.

AB . . . pressure-flow relationship during 1.0 MAC isoflurane anesthesia were studied. Mean arterial pressure (MAP) was increased by one of 3 vasopressors [**angiotensin II** (AT), norepinephrine (NE), or phenylephrine (PE)] in 3 groups of New Zealand white rabbits. Regional cerebral blood flow (CBF) was. . . vasoconstrictive effects during 1.0 MAC isoflurane anesthesia in the rabbit. The choice of vasopressor critically influences the interpretation of whether **cerebrovascular** autoregulation is intact during isoflurane anesthesia.

IT 51-41-2, Norepinephrine 59-42-7, Phenylephrine 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(brain pressure-flow relationship response to, during anesthesia)

L1 ANSWER 106 OF 123 CAPLUS COPYRIGHT 2003 ACS
1989:608891 Document No. 111:208891 Effects of ONO-3708, an antagonist of the thromboxane A2/prostaglandin endoperoxide receptor, on blood vessels. Kondo, Kigen; Seo, Rumi; Omawari, Nagashige; Imawaka, Haruo; Wakitani, Korekiyo; Kira, Heizo; Okegawa, Tadao; Kawasaki, Akiyoshi (Minase Res. Inst., Ono Pharm. Co., Ltd., Osaka, 618, Japan). European Journal of Pharmacology, 168(2), 193-200 (English) 1989. CODEN: EJPHAZ. ISSN: 0014-2999.

AB The pharmacol. properties of the TXA2/prostaglandin endoperoxide receptor antagonist ONO-3708 on blood vessels were examd. in vitro and in vivo. ONO-3708 at 10 .mu.M inhibited rabbit aortal contractions induced by TXA2, PGH2, U-46619, or PGF2.alpha. without affecting the contractions induced by **angiotensin II**, serotonin or norepinephrine. ONO-3708 at 1-100 nM was a competitive inhibitor of the contractile responses of the canine basilar artery to 9,11-epithio-11,12-methanothromboxane A2 (STA2), U-46619 and PGF2.alpha., and a noncompetitive inhibitor of the contractile responses to 15-hydroperoxyeicosatetraenoic acid (15-HPETE). In vivo ONO-3708 (10 and 100 .mu.g/kg/min i.v.) relaxed the constriction of the basilar artery induced by i.v. infusion of STA2 (0.1 .mu.g/kg/min) in cats. Infusion of ONO-3708 (10 and 30 .mu.g/kg/min i.v.) prevented the cerebral vasospasm in a **subarachnoid hemorrhage** model in dogs. ONO-3708 is a potent antagonist of the TXA2/prostaglandin endoperoxide receptor in vitro and in vivo and may be of therapeutic use in preventing cerebral vasospasms.

AB . . . at 10 .mu.M inhibited rabbit aortal contractions induced by TXA2, PGH2, U-46619, or PGF2.alpha. without affecting the contractions induced by **angiotensin II**, serotonin or norepinephrine. ONO-3708 at 1-100 nM was a competitive inhibitor of the contractile responses of the canine basilar artery. . . . of STA2 (0.1 .mu.g/kg/min) in cats. Infusion of ONO-3708 (10 and 30 .mu.g/kg/min i.v.) prevented the cerebral vasospasm in a **subarachnoid hemorrhage** model in dogs. ONO-3708 is a potent antagonist of the TXA2/prostaglandin endoperoxide receptor in vitro and in vivo and may. . .

L1 ANSWER 107 OF 123 CAPLUS COPYRIGHT 2003 ACS
1989:509555 Document No. 111:109555 Effects of two hypertensive agents, norepinephrine and **angiotensin II**, on the relation between arterial pressure and regional cerebral blood flow in conscious and anesthetized rabbits. Reynier-Rebuffel, A. M.; Aubineau, P.; Issertial, O.; Seylaz, J. (Lab. Physiol. Physiopathol. Cerebrovasc., Univ. Paris VII, Paris, 75010, Fr.). Circulation et Metabolisme du Cerveau, 6(1), 47-55 (French) 1989. CODEN: CMCEEW. ISSN: 0264-6900.

AB Regional cerebral blood flow reactivity to moderate hypertension induced by i.v. perfusion of norepinephrine or **angiotensin II** was compared in unanesthetized or anesthetized rabbits. The reactivity to each hypertensive drug varied from one region to another. Compared to control, norepinephrine induced decreases in local flow of 4 out of 11 structures examd., whereas angiotensin increased flow in the caudate nucleus. Local reactivity depended on the hypertensive agents used. Generally, in both anesthetized and unanesthetized animals, norepinephrine induced greater increases in **cerebrovascular** resistance than angiotensin. Reactivity was strongly modified by anesthesia. Under anesthesia a correlation was obsd. between regional cerebral blood flow and increases in blood pressure which did not exist in the unanesthetized group. Evidently, the mechanisms regulating regional cerebral blood flow during identical rises in blood pressure are not related to the peripheral hypertensive action of norepinephrine and angiotensin. This observation, together with the regional differences in reactivity found, both in the presence and the absence of anesthesia, suggests that these agents may exert specific effects on the cerebral circulation, more complex than myogenic or metabolic effects.

TI Effects of two hypertensive agents, norepinephrine and **angiotensin II**, on the relation between arterial pressure and regional cerebral blood flow in conscious and anesthetized rabbits

AB Regional cerebral blood flow reactivity to moderate hypertension induced by i.v. perfusion of norepinephrine or **angiotensin II** was compared in unanesthetized or anesthetized rabbits. The reactivity to each hypertensive drug varied from one region to another. Compared. . . . Local reactivity depended on the hypertensive agents used. Generally, in both anesthetized and unanesthetized animals, norepinephrine induced greater increases in **cerebrovascular** resistance than angiotensin. Reactivity was strongly modified by anesthesia. Under anesthesia a correlation was obsd. between regional cerebral blood flow. . . .

IT Anesthesia
(**angiotensin II** and norepinephrine effect on brain circulation and blood pressure in)

IT Blood pressure
(**angiotensin II** and norepinephrine effect on, in anesthesia, brain circulation in relation to)

IT Brain
(circulation of, **angiotensin II** and norepinephrine

L1 ANSWER 107 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
effect on, in anesthesia, blood pressure in relation to)

IT Blood vessel
(constriction of, by **angiotensin II** and norepinephrine, in anesthesia, brain circulation in relation to)

IT Circulation
(regional, of brain, **angiotensin II** and norepinephrine effect on, in anesthesia, blood pressure in relation to)

IT 51-41-2, Norepinephrine 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(brain circulation response to, in anesthesia, blood pressure in relation to)

L1 ANSWER 108 OF 123 CAPLUS COPYRIGHT 2003 ACS
1989:112566 Document No. 110:112566 **Cerebrovascular angiotensin II** receptors in spontaneously hypertensive rats. Grammas, Paula; Diglio, Clement; Giacomelli, Filiberto; Wiener, Joseph (Sch. Med., Wayne State Univ., Detroit, MI, USA). Journal of Cardiovascular Pharmacology, 13(2), 227-32 (English) 1989. CODEN: JCPCDT. ISSN: 0160-2446.

AB The objective of this study was to characterize **angiotensin II** (AII) receptors in cerebral capillary endothelium and to exam. whether the first step in **AII** responsiveness, namely **AII** receptor binding, is aberrant in cerebral microvessels obtained from adult spontaneously hypertensive rats (SHR). The binding of [3H]**angiotensin II** to isolated cerebrocortical microvessels from Sprague-Dawley, Wistar-Kyoto, and SHR rats was used to characterize **AII** receptors on these vessels. Kinetic expts. yielded an equil.-derived Kd (dissocn. rate const./assocn. rate const.) very close to that obtained from Scatchard anal. of satn. binding data. Thus, the two normotensive control strains exhibited comparable **AII** receptor affinity and binding capacity. In contrast, expts. with microvessels from adult SHR indicated a higher Bmax for **AII** receptors relative to controls. Although expts. assessing functional endothelial alterations in the SHR to **AII** remain to be performed, the increase in **AII** receptor no. suggests that an abnormality in vascular **AII** responsiveness may play an important role in this model of hypertension.

TI **Cerebrovascular angiotensin II** receptors in spontaneously hypertensive rats

AB The objective of this study was to characterize **angiotensin II** (AII) receptors in cerebral capillary endothelium and to exam. whether the first step in **AII** responsiveness, namely **AII** receptor binding, is aberrant in cerebral microvessels obtained from adult spontaneously hypertensive rats (SHR). The binding of [3H]**angiotensin II** to isolated cerebrocortical microvessels from Sprague-Dawley, Wistar-Kyoto, and SHR rats was used to characterize **AII** receptors on these vessels. Kinetic expts. yielded an equil.-derived Kd (dissocn. rate const./assocn. rate const.) very close to that obtained from Scatchard anal. of satn. binding data. Thus, the two normotensive control strains exhibited comparable **AII** receptor affinity and binding capacity. In contrast, expts. with microvessels from adult SHR indicated a higher Bmax for **AII** receptors relative to controls. Although expts. assessing functional endothelial alterations in the SHR to **AII** remain to be performed, the increase in **AII** receptor no. suggests that an abnormality in vascular **AII** responsiveness may play an important role in this model of hypertension.

ST **angiotensin II** receptor microvessel hypertension rat

IT Brain
(**angiotensin II** receptors of capillary endothelium of, of spontaneously hypertensive rats)

IT Rat
(**angiotensin II** receptors of cerebral capillary endothelium of spontaneously hypertensive)

L1 ANSWER 108 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT Receptors
RL: BIOL (Biological study)
(for **angiotensin II**, of cerebral capillary endothelium of spontaneously hypertensive rats)
IT Capillary vessel
(endothelium, **angiotensin II** receptors of, of brain of spontaneously hypertensive rats)
IT Hypertension
(spontaneous, **angiotensin II** receptors of cerebral capillary endothelium in, in rats)
IT 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(receptors for, of cerebral capillary endothelial of spontaneously hypertensive rats)

L1 ANSWER 109 OF 123 CAPLUS COPYRIGHT 2003 ACS
1989:107918 Document No. 110:107918 Enalapril prevents stroke and kidney dysfunction in salt-loaded stroke-prone spontaneously hypertensive rats. Stier, Charles T., Jr.; Benter, Ibrahim F.; Ahmad, Saleem; Zuo, Hailiu; Selig, Nicola; Roethel, Steven; Levine, Seymour; Itskovitz, Harold D. (Dep. Pharmacol., New York Med. Coll., Valhalla, NY, 10595, USA). Hypertension, 13(2), 115-21 (English) 1989. CODEN: HPRTDN. ISSN: 0194-911X.
AB The influence of chronic treatment with the angiotensin I converting enzyme (ACE) inhibitor enalapril on blood pressure, kidney function, and survival was examd. in stroke-prone spontaneously hypertensive rats (SHRSP). Male SHRSP that were fed a Japanese rat chow plus a 1% NaCl drinking soln. beginning at 7-8 wk of age developed severe hypertension and stroke; 14 of 18 untreated control SHRSP died by 14 wk of age and exhibited evidence of **cerebrovascular** lesions. When enalapril (15 mg/kg/day) was included in the drinking soln. of 15 SHRSP, blood pressure was initially reduced by only a slight degree, whereas survival improved markedly; only one of 10 SHRSP died before the rest were killed at 18 to 21 wk. The remaining five enalapril-treated SHRSP lived beyond 36 wk and on histol. examn. exhibited no evidence of **cerebrovascular** lesions. Chronic enalapril treatment also prevented the greater urinary excretion of protein and severe renal lesions obsd. in untreated SHRSP but did not affect urinary salt and water excretion. In anesthetized rats, glomerular filtration rate and tubular reabsorption of water were lower in untreated control SHRSP when compared with enalapril-treated SHRSP. Mean arterial pressure was comparable in both groups. These data support a possible role for ACE inhibition in the prevention of stroke and maintenance of kidney function independent of any marked change in blood pressure of SHRSP. Whether the protective effects of ACE inhibition relate to reduced **angiotensin II** formation, increased tissue kinins, or another mechanism remains to be detd.
AB . . . severe hypertension and stroke; 14 of 18 untreated control SHRSP died by 14 wk of age and exhibited evidence of **cerebrovascular** lesions. When enalapril (15 mg/kg/day) was included in the drinking soln. of 15 SHRSP, blood pressure was initially reduced by. . . to 21 wk. The remaining five enalapril-treated SHRSP lived beyond 36 wk and on histol. examn. exhibited no evidence of **cerebrovascular** lesions. Chronic enalapril treatment also prevented the greater urinary excretion of protein and severe renal lesions obsd. in untreated SHRSP. . . independent of any marked change in blood pressure of SHRSP. Whether the protective effects of ACE inhibition relate to reduced **angiotensin II** formation, increased tissue kinins, or another mechanism remains to be detd.

L1 ANSWER 110 OF 123 CAPLUS COPYRIGHT 2003 ACS
1988:448481 Document No. 109:48481 Role of angiotensin in autoregulation of cerebral blood flow. Paulson, Olaf B.; Waldemar, Gunhild; Andersen, Allan R.; Barry, David I.; Pedersen, Erik V.; Schmidt, Jes F.; Vorstrup, Sissel (Dep. Neurol., Rigshosp., Copenhagen, DK-2100, Den.). Circulation, Supplement, 77(1), I55-I58 (English) 1988. CODEN: CISUAQ. ISSN: 0069-4193.
AB A review, with 39 refs., on evidence supporting the hypothesis that locally produced **angiotensin II** contributes to **cerebrovascular** resistance and thus plays a role in autoregulation of cerebral blood flow.
AB A review, with 39 refs., on evidence supporting the hypothesis that locally produced **angiotensin II** contributes to **cerebrovascular** resistance and thus plays a role in autoregulation of cerebral blood flow.
IT Brain
(circulation of, **angiotensin II** in autoregulation of)
IT Circulation
(cerebral, autoregulation of, **angiotensin II** in)
IT 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(cerebral circulation autoregulation by)

L1 ANSWER 111 OF 123 CAPLUS COPYRIGHT 2003 ACS
1988:144167 Document No. 108:144167 Effect of **angiotensin II** and peptide YY on cerebral and circumventricular blood flow. Tuor, U. I.; Kondysar, M. H.; Harding, R. K. (Dep. Physiol., Univ. Ottawa, Ottawa, ON, K1H 8M5, Can.). Peptides (New York, NY, United States), 9(1), 141-9 (English) 1988. CODEN: PPTDD5. ISSN: 0196-9781.
AB The effect of acute i.v. infusion of saline, **angiotensin II**, or peptide YY on local cerebral blood flow ([14C]iodoantipyrine autoradiog.) in the circumventricular and noncircumventricular brain regions of conscious rats was examd. No redns. in brain blood flow (28 regions) were obsd. although **angiotensin II** and peptide YY infusion elevated arterial blood pressure 15-25% without influencing heart rate, suggesting an increase in peripheral resistance. However, local blood flow was dependent on the peptide infused. During peptide YY infusion, blood flow was rather const. in the 20 noncircumventricular regions examd., whereas an increase in blood flow and a slight decrease in **cerebrovascular** resistance occurred in the circumventricular regions. The area postrema exhibited the most pronounced changes - an elevation in blood flow of 44% and a redn. in resistance of 20% in comparison with values for control animals. During **angiotensin II** infusion, local cerebral blood flow was similar to that in controls and local **cerebrovascular** resistance was elevated. Thus, the local cerebral circulatory response to peptide administration was dependent on the location of the region examd. (circumventricular or noncircumventricular) and on the vasoactive peptide infused.
TI Effect of **angiotensin II** and peptide YY on cerebral and circumventricular blood flow
AB The effect of acute i.v. infusion of saline, **angiotensin II**, or peptide YY on local cerebral blood flow ([14C]iodoantipyrine autoradiog.) in the circumventricular and noncircumventricular brain regions of conscious rats was examd. No redns. in brain blood flow (28 regions) were obsd. although **angiotensin II** and peptide YY infusion elevated arterial blood pressure 15-25% without influencing heart rate, suggesting an increase in peripheral resistance. However, . . . was rather const. in the 20 noncircumventricular regions examd., whereas an increase in blood flow and a slight decrease in **cerebrovascular** resistance occurred in the circumventricular regions. The area postrema exhibited the most pronounced changes - an elevation in blood flow of 44% and a redn. in resistance of 20% in comparison with values for control animals. During **angiotensin II** infusion, local cerebral blood flow was similar to that in controls and local **cerebrovascular** resistance was elevated. Thus, the local cerebral circulatory response to peptide administration was dependent on the location of the region. . .
IT Blood pressure
(**angiotensin II** and peptide YY effect on, brain circulation in relation to)
IT Brain
(circulation of, **angiotensin II** and peptide YY effect on)
IT Blood vessel

L1 ANSWER 111 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
(contraction of, of brain, **angiotensin II** and peptide YY effect on)
IT Circulation
(of circumventricular and noncircumventricular regions, **angiotensin II** and peptide YY effect on)
IT Brain
(circumventricular organ, circulation of, **angiotensin II** and peptide YY effect on)
IT 11128-99-7, **Angiotensin II** 106388-42-5, Peptide YY
RL: BIOL (Biological study)
(brain circumventricular and noncircumventricular region circulation response to)

L1 ANSWER 112 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: BIOL (Biological study)
(cerebral artery relaxation by, hemolyzate inhibition of)

L1 ANSWER 112 OF 123 CAPLUS COPYRIGHT 2003 ACS
1988:144109 Document No. 108:144109 Hemolyzate inhibits cerebral artery relaxation. Toda, Noboru (Dep. Pharmacol., Shiga Univ. Med. Sci., Otsu, 520-21, Japan). Journal of Cerebral Blood Flow and Metabolism, 8(1), 46-53 (English) 1988. CODEN: JCBMDN. ISSN: 0271-678X.
AB In helical strips of dog middle cerebral arteries partially contracted with PGF2.alpha., relaxations induced by **angiotensin II**, possibly mediated by PGI2, and those induced by PGH2 were reversed to a contraction or markedly reduced by treatment with hemolyzate, which, however, attenuated the PGI2-induced relaxation only slightly. The relaxant response of human middle cerebral arterial strips to PGH2 was also suppressed by hemolyzate. Dog and monkey middle cerebral arteries responded to transmural elec. stimulation and nicotine with transient relaxations, which were quite susceptible to tetrodotoxin and hexamethonium, resp.; the relaxations were abolished almost completely by hemolyzate and methylene blue. One the other hand, the relaxant response of dog cerebral arteries to a low concn. of K+ was not influenced by hemolyzate or by methylene blue, but was reversed to a contraction by treatment with ouabain. Relaxations induced by substance P and nitroglycerin were markedly inhibited by hemolyzate; removal of endothelium abolished the relaxation by substance P, but did not influence the nitroglycerin-induced relaxation. Hemolyzate may interfere with the biosynthesis of PGI2 in the vascular wall, thereby reversing the relaxation induced by **angiotensin II** and PGH2 to a contraction. Relaxations induced by elec. and chem. stimulation of vasodilator nerves innervating cerebral arteries appear to be elicited by a mechanism dependent on cellular cGMP, like that underlying the substance P-induced and nitroglycerin-induced relaxation. These actions of hemolyzate may be involved in the genesis of cerebral vasospasm after **subarachnoid hemorrhage**.
AB In helical strips of dog middle cerebral arteries partially contracted with PGF2.alpha., relaxations induced by **angiotensin II**, possibly mediated by PGI2, and those induced by PGH2 were reversed to a contraction or markedly reduced by treatment with. . . nitroglycerin-induced relaxation. Hemolyzate may interfere with the biosynthesis of PGI2 in the vascular wall, thereby reversing the relaxation induced by **angiotensin II** and PGH2 to a contraction. Relaxations induced by elec. and chem. stimulation of vasodilator nerves innervating cerebral arteries appear to. . . the substance P-induced and nitroglycerin-induced relaxation. These actions of hemolyzate may be involved in the genesis of cerebral vasospasm after **subarachnoid hemorrhage**.
IT Meninges
(diseases, **subarachnoid hemorrhage**, vasospasm after, cerebral artery relaxation by hemolyzate in relation to)
IT 54-11-5, Nicotine 55-63-0, Nitroglycerin 7440-09-7, Potassium, biological studies 11128-99-7, **Angiotensin II** 33507-63-0, Substance P 42935-17-1, PGH2

L1 ANSWER 113 OF 123 CAPLUS COPYRIGHT 2003 ACS
1988:69671 Document No. 108:69671 **Cerebrovascular** reactivity to angiotensin and angiotensin-converting enzyme activity in cerebrospinal fluid. Whalley, E. T.; Wahl, M. (Dep. Physiol., Univ. Munich, Munich, D-8000/2, Fed. Rep. Ger.). Brain Research, 438(1-2), 1-7 (English) 1988. CODEN: BRREAP. ISSN: 0006-8993.
AB The vasomotor effects of angiotensin I (A I) and **angiotensin II** (A II) were examd. in feline cerebral arteries and angiotensin-converting enzyme (ACE) activity was detd. in the vessel wall and cerebrospinal fluid (CSF). A II (10-8-10-5M) induced concn.-dependent contractions of feline pial arteries (resting diam., 98-286 .mu.m) in situ with a max. of 34% at 10-4M A II. A I produced dose-related contractions being approx. 20 times less potent than A II. The action of A I was attenuated by the ACE inhibitor captopril (10-5M). These findings demonstrate the presence of ACE activity in the vessel wall and/or its surroundings. ACE activity was also found in feline CSF sampled from the cisterna cerebello-medullaris. Bradykinin (BK) was broken down and A I converted to A II by CSF, both effects being inhibited by captopril. This was demonstrated using bioassay and HPLC. Thus, the presence of ACE in the vessel wall and CSF is necessary for the conversion of A I to A II. Although ACE in CSF is able to degrade BK, it appears not to be important for the metab. of BK acting from the perivascular side of pial arteries in situ.
TI **Cerebrovascular** reactivity to angiotensin and angiotensin-converting enzyme activity in cerebrospinal fluid
AB The vasomotor effects of angiotensin I (A I) and **angiotensin II** (A II) were examd. in feline cerebral arteries and angiotensin-converting enzyme (ACE) activity was detd. in the vessel wall and. . .
IT Cerebrospinal fluid
(angiotensin-converting enzyme of, **cerebrovascular** response to angiotensins in relation to)
IT 9041-90-1, Angiotensin I 11128-99-7, **Angiotensin II**
RL: BIOL (Biological study)
(**cerebrovascular** response to, angiotensin-converting enzyme of cerebrospinal fluid in relation to)
IT 9015-82-1, Angiotensin converting enzyme
RL: BIOL (Biological study)
(of cerebral blood vessels and cerebrospinal fluid, angiotensins **cerebrovascular** effects in relation to)

L1 ANSWER 114 OF 123 CAPLUS COPYRIGHT 2003 ACS
1987:513591 Document No. 107:113591 Nonuniformity of CBF response to NE- or ANG II-induced hypertension in rabbits. Reynier-Rebuffel, Anne Marie; Aubineau, Pierre; Issertial, Odile; Seylaz, Jacques (Lab. Physiol. Physiopathol. Cerebrovasc., Fac. Med., Paris, 75010, Fr.). American Journal of Physiology, 253(1, Pt. 2), H47-H57 (English) 1987. CODEN: AJPHAP. ISSN: 0002-9513.

AB The regional response of brain vasculature to moderate hypertension was investigated using 2 hypertensive drugs norepinephrine (NE) and **angiotensin II** (ANG II), infused i.v. at low concns. (increase in blood pressure 15-40 mmHg). Regional cerebral blood flow was measured in unanesthetized and anesthetized rabbits using the [14C] ethanol satn. technique. In both groups of animals, NE and ANG II induced regional differences in the flow changes as compared with controls, confirming a regional (or segmental) heterogeneity in the regulatory mechanisms to hypertension. The responses to identical rises in blood pressure (BP) in most of the structures analyzed depended on the drug used. In the unanesthetized rabbits, the increase in vascular resistance induced by NE was greater than that induce by ANG II. With the 2 drugs, there was no correlation between the flow changes in any of the structures considered and either the BP increase or the BP level in unanesthetized animals. However, these flow changes were correlated with the BP increase in anesthetized animals, although differences between the effects of NE and ANG II were again obsd. Apparently, **cerebrovascular** regulatory mechanisms in hypertension are probably more complex than a simple myogenic reaction. Their heterogeneity and their dependence both on the cause of hypertension and on the presence of anesthetics suggest the intervention of an integrating pathway.

AB The regional response of brain vasculature to moderate hypertension was investigated using 2 hypertensive drugs norepinephrine (NE) and **angiotensin II** (ANG II), infused i.v. at low concns. (increase in blood pressure 15-40 mmHg). Regional cerebral blood flow was measured in. . . the BP increase in anesthetized animals, although differences between the effects of NE and ANG II were again obsd. Apparently, **cerebrovascular** regulatory mechanisms in hypertension are probably more complex than a simple myogenic reaction. Their heterogeneity and their dependence both on. . .

ST brain blood flow norepinephrine hypertension; **angiotensin II** hypertension brain blood flow

IT Brain
(circulation in regions of, in hypertension induced by **angiotensin II** or norepinephrine, nonuniformity of)

IT Hypertension
(from **angiotensin II** or norepinephrine, circulation in brain regions in, nonuniformity of)

IT Anesthesia
(in brain regional blood flow nonuniform response to hypertension induced by **angiotensin II** or norepinephrine)

L1 ANSWER 114 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT Circulation
(of brain regions, in hypertension induced by **angiotensin II** or norepinephrine, nonuniformity of)

L1 ANSWER 115 OF 123 CAPLUS COPYRIGHT 2003 ACS
1987:189820 Document No. 106:189820 Specific binding of atrial natriuretic factor in brain microvessels. Chabrier, Pierre E.; Roubert, Pierre; Braquet, Pierre (Res. Lab., Inst. Henri Beaufour, Les Ulis, 91940, Fr.). Proceedings of the National Academy of Sciences of the United States of America, 84(7), 2078-81 (English) 1987. CODEN: PNASA6. ISSN: 0027-8424.

AB The binding of 125I-labeled rat atrial natriaretic factor (99-126) (I) [88898-17-3] to pure bovine cerebral microvessel prepns. was examd. Satn. and competition expts. demonstrated the presence of a single class of I-binding sites with high affinity (dissocn. const., .apprx.10-10M) and with a binding capacity of 58 fmol/mg of protein. The binding of radioiodinated I to brain microvessels was specific, reversible, and time dependent, as was shown by assocn.-dissocn. expts. The demonstration of specific I-binding sites on brain microvessels supposes a physiol. role of I on brain microvasculature. The coexistence of I and **angiotensin II** receptors on this **cerebrovascular** tissue suggests that the 2 circulating peptides may act as mutual antagonists in the regulation of brain microcirculation and(or) blood-brain barrier function.

AB . . . specific I-binding sites on brain microvessels supposes a physiol. role of I on brain microvasculature. The coexistence of I and **angiotensin II** receptors on this **cerebrovascular** tissue suggests that the 2 circulating peptides may act as mutual antagonists in the regulation of brain microcirculation and(or) blood-brain. . .

L1 ANSWER 116 OF 123 CAPLUS COPYRIGHT 2003 ACS
1985:516893 Document No. 103:116893 Intrinsic and extrinsic mechanisms involved in the **cerebrovascular** reaction elicited by immobilization stress in rabbits. Pinard, E.; Lacombe, P.; Reynier-Rebuffel, A. M.; Seylaz, J. (Lab. Physiol. Physiopathol. Cerebrovasc., Univ. Paris VII, Paris, Fr.). Brain Research, 340(2), 305-14 (English) 1985. CODEN: BRREAP. ISSN: 0006-8993.

AB Variations in cerebral blood flow pO2, and pCO2 were studied in rabbits during short-duration (1-min) immobilization stress. The techniques were used to det. these variables locally in the caudate nucleus in a continuous, simultaneous, and quant. fashion. Cerebral blood flow and arterial blood pressure increased in parallel immediately after inducing the stress reaction, and that pO2 increased further, indicating that cerebral O supply is maintained by the hyperemia. Previous administration of a .beta.-receptor blocker or of a cholinergic receptor blocker significantly diminished the **cerebrovascular** reaction to stress, inducing a decrease in pO2 during the reaction. Administration of both blockers nearly abolished the cerebral vasodilation studied. Previous administration of an .alpha.-receptor blocker enhanced the reactive hyperemia. No disturbance of the blood-brain barrier could be obsd. in rabbits subjected to stress. Injection of adrenaline [51-43-4], as well as **angiotensin II** [11128-99-7] inducing similar increases in blood pressure, had no comparable effect on the blood flow. In this model of anxiety, neurogenic mechanisms are evidently involved in the provision of a sufficient O supply to the brain.

TI Intrinsic and extrinsic mechanisms involved in the **cerebrovascular** reaction elicited by immobilization stress in rabbits

AB . . . is maintained by the hyperemia. Previous administration of a .beta.-receptor blocker or of a cholinergic receptor blocker significantly diminished the **cerebrovascular** reaction to stress, inducing a decrease in pO2 during the reaction. Administration of both blockers nearly abolished the cerebral vasodilation. . . disturbance of the blood-brain barrier could be obsd. in rabbits subjected to stress. Injection of adrenaline [51-43-4], as well as **angiotensin II** [11128-99-7] inducing similar increases in blood pressure, had no comparable effect on the blood flow. In this model of anxiety, . . .

ST receptor **cerebrovascular** restraint stress; circulation brain restraint stress receptor

IT Receptors
RL: BIOL (Biological study)
(cholinergic, **cerebrovascular** systems in restraint stress regulation by)

IT Stress, biological
(restraint, **cerebrovascular** system in, receptor regulation of)

IT Receptors
RL: BIOL (Biological study)
(.alpha.-adrenergic, **cerebrovascular** systems in restraint stress regulation by)

IT Receptors
RL: BIOL (Biological study)
(.beta.-adrenergic, **cerebrovascular** systems in restraint

L1 ANSWER 116 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
stress regulation by)

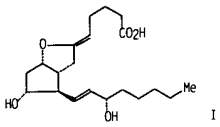
L1 ANSWER 117 OF 123 CAPLUS COPYRIGHT 2003 ACS
1985:179799 Document No. 102:179799 Cerebral vasomotor action of **angiotensin II**. Reynier-Rebuffel, A. M.; Aubineau, P. F.; Pinard, E.; Meric, P.; Seylaz, J. (Lab. Physiol. Physiopathol. Cerebrovasc., Univ. Paris VII, Paris, 75010, Fr.). Circulation et Metabolisme du Cerveau, 1(3), 251-8 (French) 1984. CODEN: CMCEEW. ISSN: 0264-6900.
AB Unilateral infusion of **angiotensin II** [11128-99-7] into the carotid artery of rabbits produced a generalized decrease in cerebral blood flow with a rise in **cerebrovascular** resistance of 13-41% depending on the area examd. Evidently, **angiotensin II** has an indirect action on **cerebrovascular** motricity.
TI Cerebral vasomotor action of **angiotensin II**
AB Unilateral infusion of **angiotensin II** [11128-99-7] into the carotid artery of rabbits produced a generalized decrease in cerebral blood flow with a rise in **cerebrovascular** resistance of 13-41% depending on the area examd. Evidently, **angiotensin II** has an indirect action on **cerebrovascular** motricity.
ST **angiotensin II** circulation brain
IT Brain
(circulation of, **angiotensin II** effect on)
IT Blood vessel
(motricity of, of brain cerebrum, **angiotensin II** effect on)
IT Circulation
(of brain, **angiotensin II** effect on)

L1 ANSWER 118 OF 123 CAPLUS COPYRIGHT 2003 ACS
1985:89883 Document No. 102:89883 **Cerebrovascular** aspects of converting-enzyme inhibition. I: effects of intravenous captopril in spontaneously hypertensive and normotensive rats. Barry, David I.; Jarden, Jens O.; Paulson, Olaf B.; Graham, David I.; Strandgaard, Svend (Dep. Psychiatry, Rigshosp., Copenhagen, DK-2100, Den.). Journal of Hypertension, 2(6), 589-97 (English) 1984. CODEN: JOHYD3. ISSN: 0263-6352.
AB The **cerebrovascular** effects of angiotensin-converting enzyme [9015-82-1] inhibition were examd. in normotensive and hypertensive rats. Cerebral blood flow was measured using the intracarotid 133Xe injection method in halothane/N2O-anesthetized animals. Following i.v. administration of captopril [62571-86-2] (10 mg/kg), cerebral blood flow autoregulation was markedly altered. Although cerebral blood flow was unchanged from baseline levels, both the lower and upper limits of autoregulation were reset to lower mean arterial pressure and the autoregulatory plateau was shortened. The lower limit was shifted 20-30 mm Hg, the upper limit 50-60 mm Hg, and the plateau shortened by 20-40 mm Hg. The effect resulted from compensatory autoregulatory constriction of small resistance vessels in the brain following captopril-induced dilatation of large resistance vessels. Thus, locally produced **angiotensin II** might play a role in the resistance of large cerebral arteries.
TI **Cerebrovascular** aspects of converting-enzyme inhibition. I: effects of intravenous captopril in spontaneously hypertensive and normotensive rats
AB The **cerebrovascular** effects of angiotensin-converting enzyme [9015-82-1] inhibition were examd. in normotensive and hypertensive rats. Cerebral blood flow was measured using the. . . compensatory autoregulatory constriction of small resistance vessels in the brain following captopril-induced dilatation of large resistance vessels. Thus, locally produced **angiotensin II** might play a role in the resistance of large cerebral arteries.

L1 ANSWER 119 OF 123 CAPLUS COPYRIGHT 2003 ACS
1983:465089 Document No. 99:65089 Generalized cerebral vasoconstriction induced by intracarotid infusion of **angiotensin II** in the rabbit. Reynier-Rebuffel, Anne Marie; Pinard, Elisabeth; Aubineau, Pierre Frederic; Meric, Philippe; Seylaz, Jacques (Lab. Physiol. Physiopathol. Cerebrosvasc., Univ. Paris VII, Paris, 75010, Fr.). Brain Research, 269(1), 91-101 (English) 1983. CODEN: BRREAP. ISSN: 0006-8993.
AB The influence of **angiotensin II** (I) [11128-99-7], perfused into 1 common carotid artery at 0.065 .mu.g/kg/min, on **cerebrovascular** resistance was investigated in the anesthetized rabbit by complementary in vivo methods. Heat clearance and mass spectrometry measurements indicated that in the homolateral caudate nucleus I decreased local blood flow (18.2%), decreased pO2 (14.2%), and had no effect on pCO2. The [14C]EtOH tissue sampling technique revealed a decrease in flow in all 10 structures sampled in the brain. This decrease was similar in magnitude in both the ipsilateral and the contralateral hemisphere with regard to the site of injection. When expressed in terms of **cerebrovascular** resistance (CVR) and allowing for a slight increase in blood pressure (<10%), these results show that I infusion induced an increase in CVR of 18-32%. Thus, a unilateral intracarotid infusion of a low dose of I induces an increased vascular tone in all cerebral structures and this action, being bilateral, cannot readily be explained by a direct action of I on the cerebral vessels in view of the very low recirculating concn. of I. The hypothesis of a cerebral vasomotor influence of I by action on a central structure is discussed.
TI Generalized cerebral vasoconstriction induced by intracarotid infusion of **angiotensin II** in the rabbit
AB The influence of **angiotensin II** (I) [11128-99-7], perfused into 1 common carotid artery at 0.065 .mu.g/kg/min, on **cerebrovascular** resistance was investigated in the anesthetized rabbit by complementary in vivo methods. Heat clearance and mass spectrometry measurements indicated that. . . in both the ipsilateral and the contralateral hemisphere with regard to the site of injection. When expressed in terms of **cerebrovascular** resistance (CVR) and allowing for a slight increase in blood pressure (<10%), these results show that I infusion induced an. . .
ST **angiotensin II cerebrovascular** resistance:
brain circulation **angiotensin II**: vasoconstriction
brain **angiotensin II**
IT Blood vessel
(constriction of, from **angiotensin II** in brain cerebrum)
IT Circulation
(of brain cerebrum, **angiotensin II** effect on)

L1 ANSWER 120 OF 123 CAPLUS COPYRIGHT 2003 ACS
1982:557186 Document No. 97:157186 Prostacyclin and cerebral vessel relaxation. Paul, Kamal S.; Whalley, Eric T.; Forster, Christine; Lye, Richard; Dutton, John (Manchester R. Infirm., Univ. Manchester, Manchester, UK). Journal of Neurosurgery, 57(3), 334-40 (English) 1982. CODEN: JONSAC. ISSN: 0022-3085.

GI



I

AB The ability of prostacyclin (I) [35121-78-9] to reverse contractions of human basilar arteries in vitro that were induced by a wide range of substances implicated in the etiol. of cerebral arterial spasm was examd. I (10-10-10-6M) caused a dose-related reversal of contractions induced by 5-HT [50-67-9], noradrenaline [51-41-2], **angiotensin II** [11128-99-7], PGF2.alpha. [551-11-1], and U-46619 [56985-40-1]. These agents were tested at concns. or vols. that produced almost max. or max. responses and those that produced approx. 50% of the max. response. Contractions induced by max. concns. of **angiotensin II** and U-46619 were least affected by I. In addn., contractions induced by TXA2 [57576-52-0] generated from guinea pig lung were reversed in a dose-dependent fashion by I. This ability of I to physiol. antagonized contractions of the human basilar artery in vitro induced by high concns. of various spasmogenic agents suggests that such a potent vasodilator agent or more stable analog may be of value in the treatment of such disorders as cerebral arterial spasm following **subarachnoid hemorrhage**.

AB . . . of cerebral arterial spasm was examd. I (10-10-10-6M) caused a dose-related reversal of contractions induced by 5-HT [50-67-9], noradrenaline [51-41-2], **angiotensin II** [11128-99-7], PGF2.alpha. [551-11-1], and U-46619 [56985-40-1]. These agents were tested at concns. or vols. that produced almost max. or max. responses and those that produced approx. 50% of the max. response. Contractions induced by max. concns. of **angiotensin II** and U-46619 were least affected by I. In addn., contractions induced by TXA2 [57576-52-0] generated from guinea pig lung were. . . agent or more stable analog may be of value in the treatment of such disorders as cerebral arterial spasm following **subarachnoid**

L1 ANSWER 120 OF 123 CAPLUS COPYRIGHT 2003 ACS (Continued)
**hemorrhage**.

L1 ANSWER 121 OF 123 CAPLUS COPYRIGHT 2003 ACS
1982:538371 Document No. 97:138371 Reversal of experimental acute cerebral vasospasm by angiotensin converting enzyme inhibition. Andrews, Philip; Papadakis, Nicholas; Gavras, Haralambos (Dep. Med., Boston Univ., Boston, MA, 02118, USA). Stroke, 13(4), 480-3 (English) 1982. CODEN: SJCCA7. ISSN: 0039-2499.

AB teprotide [35115-60-7], An angiotensin converting enzyme inhibitor, partially or totally reversed the acute arterial spasm induced in dogs by intracisternal introduction of autologous blood. Thus, **angiotensin II** [11128-99-7] may play a role in the cerebral vasospasm obsd. following introduction of blood into the subarachnoid space and converting enzyme inhibitors may be clin. useful in the prevention or reversal of cerebral arterial spasm following **subarachnoid hemorrhage**.

AB . . . enzyme inhibitor, partially or totally reversed the acute arterial spasm induced in dogs by intracisternal introduction of autologous blood. Thus, **angiotensin II** [11128-99-7] may play a role in the cerebral vasospasm obsd. following introduction of blood into the subarachnoid space and converting enzyme inhibitors may be clin. useful in the prevention or reversal of cerebral arterial spasm following **subarachnoid hemorrhage**.

ST angiotensin vasospasm **subarachnoid hemorrhage**; teprotide brain vasospasm inhibition

IT Artery, disease or disorder
(spasm, from **subarachnoid hemorrhage**, teprotide prevention of)

IT 11128-99-7
RL: BIOL (Biological study)
(in vasospasm from **subarachnoid hemorrhage**)

IT 35115-60-7
RL: BIOL (Biological study)
(vasospasm from **subarachnoid hemorrhage** prevention by)

L1 ANSWER 122 OF 123 CAPLUS COPYRIGHT 2003 ACS
1982:504042 Document No. 97:104042 Reversal of experimental delayed cerebral vasospasm by angiotensin-converting enzyme inhibition. Gavras, Haralambos; Andrews, Philip; Papadakis, Nicholas (Boston City Hosp., Boston Univ., Boston, MA, USA). Journal of Neurosurgery, 55(6), 884-8 (English) 1981. CODEN: JONSAC. ISSN: 0022-3085.

AB Delayed cerebral arterial spasm was documented by angiog. 72 h after introduction of blood in the subarachnoid space of dogs. Following injection of the angiotensin-converting enzyme inhibitor, teprotide (I) [35115-60-7], repeat cineangiograms at 30, 60, and 90 min demonstrated partial or total release of spasm of the basilar artery and its branches. Thus **angiotensin II** [11128-99-7] participates in the delayed cerebral vasospasm after hemorrhage, and angiotensin inhibition may release the spasm and prevent cerebral ischemia.

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ST cerebral vasospasm **subarachnoid hemorrhage** teprotide; angiotensin converting enzyme cerebral vasospasm

IT Hemorrhage
(subarachnoid, vasospasm from, teprotide reversal of, **angiotensin II** in relation to)

IT Artery, disease or disorder
(cerebral, spasm, from **subarachnoid hemorrhage**, teprotide reversal of, **angiotensin II** in relation to)

IT Brain, disease or disorder
(vasospasm, from **subarachnoid hemorrhage**, teprotide reversal of, **angiotensin II** in relation to)

IT 11128-99-7
RL: BIOL (Biological study)
(cerebral vasospasm from **subarachnoid hemorrhage** in relation to)

IT 35115-60-7
RL: BIOL (Biological study)
(cerebral vasospasm from **subarachnoid hemorrhage** reversal by, **angiotensin II** in relation to)

L1 ANSWER 123 OF 123 CAPLUS COPYRIGHT 2003 ACS
1982:46604 Document No. 96:46604 The effect of inhibition of dopamine-.beta.-hydroxylase on **cerebrovascular** carbon dioxide and autoregulation. Kobayashi, S.; Kitamura, A.; Furuhashi, N.; Kanda, T.; Tazaki, Y. (Dep. Internal Med., Shimane Med. Univ., Izumo, 693, Japan). Pathophysiol. Pharmacother. Cerebrovasc. Disord., Satell. Symp., 2nd, 48-51. Editor(s): Betz, E.; Grote, J.; Heuser, D. Witzstrock: Baden-Baden, Fed. Rep. Ger. (English) 1980. CODEN: 46SXAH.

AB To det. the importance of the noradrenergic nervous system for the regulation of CO2 reactivity and autoregulation, the effect of fusaric acid, a dopamine .beta.-hydroxylase inhibitor, was studied in cats. The increase of thalamic blood flow in response to raised arterial CO2 (induced by inhalation of 5% CO2) was greater after than before fusaric acid infusion. The CO2 reactivity index increased from 4.74 to 8.31, with no increase in mean arterial blood pressure. In hypotension induced by exsanguination, the autoregulation index decreased in both the subcortex and medulla in response to fusaric acid. In hypertension induced by **angiotensin II**, fusaric acid altered, neither medullary blood flow nor the autoregulation index. Thus, the noradrenergic system may have an inhibitory action in **cerebrovascular** dilation during hypercapnia, and may participate in **cerebrovascular** autoregulation during hypotension.

TI The effect of inhibition of dopamine-.beta.-hydroxylase on **cerebrovascular** carbon dioxide and autoregulation

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